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NUTRITIONAL FACTORS IN GRAVES' DISEASE *

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THAT marked grades of malnutrition may result from thyrotoxicosis has been long known. In 1893 it was that Friedrich Müller [1] noted the paradox of weight loss in the face of increased food intake and concluded therefrom that there must be in this disease an increased rate of katabolism.

Whether or not weight loss or general wasting will occur in Graves' disease depends on whether the appetite increase causes sufficient increase in the ingestion of total calories to offset the increased combustion. Compensatory hyperorexia we may call it. The bank balance, in other words, is determined by the relation of amounts deposited to those withdrawn. In Graves' disease we not infrequently encounter weight losses of as much as 50 pounds or more.

Not only, however, may thyrotoxicosis cause malnutrition, but lately it has come to our attention that malnutrition may cause, or precipitate, thyrotoxicosis.

A few years ago one of us (S. H.) was impressed with the number of patients with toxic goiter who gave histories of having started their thyrotoxic symptoms at the conclusion of a reduction program for obesity. An overweight person would go on a low calory diet and after having lost the desired amount of weight would increase the diet, but find that weight loss continued, perhaps at an accelerated rate. Along with this, nervousness, tremor and other symptoms of thyrotoxicosis would make their appearance. In some of these cases thyroid had been used to augment weight reduction, but in others, mere calory restriction.

Interest having been aroused in this sequence of events, we began to be on the lookout for such cases. They have turned out to be numerous. The total to date is 35. In 14 of these the prethyrotoxic weight loss was occa-

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sioned by reduction cures and in the remainder it was due to a variety of conditions such as restriction of diet in the treatment of ulcer, ulcerative colitis, diabetes and other diseases leading to malnutrition.

It seems to us that this series is too large not to be of significance. Episodes which activate thyrotoxicosis have long been recognized. Psychic traumata, prolonged infections, accidents or physiologic strains, such as puberty, pregnancy or the menopause, fall in this category. Now it seems that acute malnutrition can be added. How it operates, we are not prepared to say, but it is not known how any of the others operate for that matter. It may be associated with changes in blood chemistry or with vitamin or protein deficiency.

In approaching the problem of the inroads which nutritional factors may play in the production of the clinical picture in Graves' disease it will be convenient to distinguish between what we may term general malnutrition due to total negative calory balance and more specific types of malnutrition, or deficiency due to absolute or relative shortage of specific dietary elements. Of general malnutrition, save insofar as it constitutes an indication for treatment, I need say nothing further, it being thoroughly familiar. Certain specific or special types of malnutrition, on the other hand, I believe can be discussed with some profit.

In this group of special forms of malnutrition let us consider first the *musculature*. Myasthenia is a common symptom in toxic goiter. Plummer,[2] Lahey [3] and others have devised diagnostic tests to bring this symptom or sign into evidence. Actual muscle atrophy occurs less commonly, but in certain cases is very striking. Some years ago we [4] reported a case in which there was a picture closely resembling progressive muscular atrophy in an advanced stage. The patient was also found to be suffering from toxic goiter. Cure of the latter by surgery was followed by recovery of the muscles. This is the most marked example of muscle atrophy we have seen in toxic goiter, but very often we encounter lesser grades with atrophy of the temporal, interossei or shoulder girdle muscles. Such atrophy is usually present in a patient who has been severely thyrotoxic over a long period of time and is therefore of prognostic significance. The exophthalmos, in certain types at least, may be a local expression of general muscle weakness. The degenerative changes in the striated recti muscles of the eye and the normal appearance of the smooth muscle of the eye, described by Askanazy,[5] suggest a muscle imbalance which may explain exophthalmos. On the chemical side there is a disturbance in creatinine metabolism with creatinuria and, as shown by Shorr and Richardson [6] a decreased creatine tolerance test.

The skeleton in certain cases shows marked decalcification. This is properly to be classed under specific forms of inanition. Aub and his coworkers [7] in 1929 showed that the thyroid hormone causes a marked increase in the rate of withdrawal of calcium and phosphorus from the skeleton, without, however, in contrast to the parathyroid hormone, any sig-

nificant change in the blood levels of these elements. It is indeed in thyrotoxic persons that the highest levels of calcium and phosphorus excretion are to be found. This high excretion is a specific effect of the hyperthyroidism, not merely a feature of elevated general metabolism, for Aub et al.

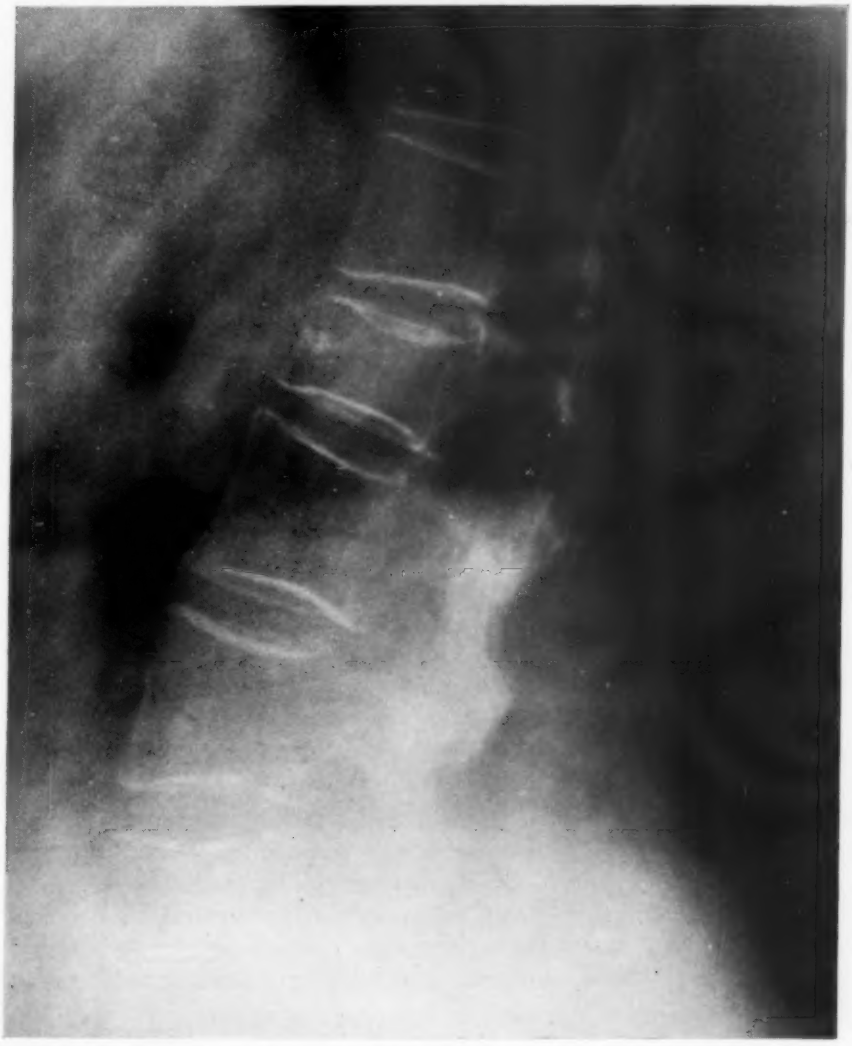

FIG. 1. Osteoporosis with compression fracture of a lumbar vertebra following thyrotoxicosis.

found in cases of fever and leukemia with marked elevation in general metabolism, normal elimination of calcium.

The rate of decalcification of the skeleton in thyrotoxicosis will depend not alone on the rate of calcium loss, but upon the intake. Although the

increase in calcium excretion is great, it usually takes a long time for osteoporosis to become apparent. Patients with acute forms of toxic goiter usually get treated successfully before any marked grade of osteoporosis has been produced. The increased appetite probably causes an increased ingestion of calcium and offsets to some extent the process of bone wasting.

In a few cases of long-standing thyrotoxicosis, however, we have observed very marked osteoporosis, both in the spine and in long bones. In some of these cases symptoms have resulted, taking the form of deep aching pain in the extremities or back, and in one remarkable case there was a pathologic fracture of the body of a vertebra. This patient had been treated by us [8] in 1919 for mild Graves' disease, then of three years' duration, by means of roentgen-ray therapy. She had improved somewhat, but, since she had not recovered completely, a subtotal thyroidectomy was done in March 1922. After that she was fairly well until August 1931, when while driving her car she was seized with sudden knife-like pain in the region of her lumbar spine. This persisted intensely and continuously for one and a half hours, then upon motion for three to four weeks, and finally as tenderness in the lumbar region until December 1, 1931, when she returned to the hospital for study. Roentgen-ray examination showed marked decalcification of the entire spine and pelvis and a compression fracture of the first lumbar vertebra. The body was half its natural thickness and was irregular and mushroomed.

The patient was put on a high calcium diet with 5 drachms of calcium glycerophosphate and 30 drops of viosterol per day, under which regime her symptoms were quickly relieved. We have followed her since and although by roentgen-ray there is no great evidence of recalcification, the symptomatic result has been excellent.

Another striking example (a private patient of J. L.) is that of a woman of 58, who became bedridden as a result of long-standing thyrotoxicosis and cardiac failure. She showed a marked degree of osteoporosis. As a result of her semi-sitting position, she developed a dorsal kyphos and flaring of the lower ribs. The latter were exquisitely tender to pressure.

With removal of the thyroid, she has gradually assumed her normal activities and her heart is well compensated. Her kyphos has straightened considerably, the flaring of the rib margins is less and tenderness has disappeared. She is on an adequate diet with emphasis on milk, vegetables, cheese and meat.

In cases of long-standing thyrotoxicosis then, or even past thyrotoxicosis, in which pains in the spine or extremities are complained of, the possibility of osteoporosis should be given consideration and, if found, suitable treatment by a recalcifying regime instituted.

A shortage of iron is suggested in an impressive number of patients with thyrotoxicosis by the presence of nail changes of the sort characteristic of hypochromic anemia—that is to say spoon-shaped, brittle, lustreless and

longitudinally ridged—together with smooth tongues and gastric achlorhydria. Even when these signs are well marked, one usually finds but a slight degree of anemia. One patient recently, however, a woman of 58, presented symptoms of thyrotoxicosis, minimal eye signs and goiter, basal metabolic rate at the level of about plus 40 and along with all this, smooth tongue, spoon fingernails, achlorhydria, red count of 3.6 million and hemoglobin of 45 per cent. She was placed on both iodine and iron. She made a characteristic and good response symptomatically and metabolically to iodine, her basal metabolic rate falling to standard in nine days. She was continued on iodine for a year at the end of which time her basal metabolic rate was normal and she was symptom-free. The anemia also, in less than a month, rose to a red cell level of 6 million and hemoglobin of 75 per cent. Iron was then omitted. We presume that iron was responsible for the result. At the end of a year her blood picture showed a red cell count of 4.8 million and hemoglobin of 85 per cent.

Of late we have been interested in the question of avitaminosis in thyrotoxicosis. In the case of vitamin B_1, at least, Cowgill and his co-workers [9] and others have shown that the need for vitamin increases in parallel fashion to the metabolic rate. Thus a person who had been receiving an adequate amount of vitamin B_1 during health might develop a deficiency on the same vitamin intake if he became thyrotoxic.

In view of these facts, two of us (S. H. and J. L.) administered vitamin B_1 in the form of Harris Yeast Powder to a small series of thyrotoxic patients and found that although it caused no change in basal metabolic rate, there was, coincident with its administration, a marked improvement in appetite and consequent gain in weight. Since that time we have employed treatment with yeast routinely in the preparation of thyrotoxic patients for operation. Although it is too early to draw a conclusion based on statistics of the effect of this maneuver on operative mortality, it is becoming increasingly clear that it is of value in improving general nutrition through the increase it causes in appetite. Its use is chiefly indicated in those patients whose appetite increase has been inadequate.

Shortage of vitamin B_1 may also play a more specific rôle in thyrotoxicosis. Weiss [10] has shown that in alcoholics with cardiac insufficiency avitaminosis B_1 may play a rôle. It is quite possible, as he suggested to us, that it may also play a rôle in the cardiac insufficiency of thyrotoxicosis. Certainly one is more apt to see cardiac insufficiency in the malnourished than in the well nourished thyrotoxic patient. We recalled four recent striking examples as soon as Weiss mentioned the matter to us. One of these also had a moderate hypochromic anemia. Since iodine produces benefit in nearly any thyrotoxic patient, and since it is our practice not to withhold iodine in the thyrotoxic patient with cardiac insufficiency, we cannot say with certainty how much, if any, benefit to the heart vitamin B_1 administration has conferred per se. It will only be after large numbers have been treated that a dependable conclusion can be drawn.

Evidence of shortage of other vitamins has not been impressive. Scurvy we have not seen, but in one recent case in which thyrotoxicosis followed a grossly inadequate diet, night blindness became a striking symptom. It cleared up directly when an adequate diet was received. It may be interpreted as evidence of a shortage of vitamin A.

The chief point which we wish to make about all these matters, is that there is much more to the preparation of the thyrotoxic patient for operation than mere iodinization. The preparation, which we believe should be under the direction of the physician, but observed also by the surgeon, should include a positive attempt to improve general nutrition and relieve any specific deficiencies insofar as this is possible. Sometimes it will be the part of wisdom to defer operation, even though a good iodine response has been obtained, in order to meet more adequately a nutritional indication. The following case is a good example.

A 43 year old widowed supervisor of nurses, who had acute rheumatic fever at the age of 28, followed by mitral stenosis, entered the medical ward February 16, 1936, with a story that for two years or more she had been running herself ragged, eating very little, taking a great excess of tea and coffee, sleeping badly, having marked anorexia and losing in 18 months some 25 pounds. She had been a thin, frail woman to start with and after the loss mentioned was markedly malnourished.

For two months prior to entry in addition there had been marked nervous irritability. At the time of entry she showed marked hyperirritability, slight bilateral exophthalmos, marked tremor, warm moist skin, tachycardia of 140, slight diffuse enlargement of the thyroid and a basal metabolic level of plus 30. Her heart showed the murmur characteristic of mitral stenosis, with normal rhythm. She weighed 106 pounds. Her tongue was sore and atrophic, but there was no anemia. Her red count was 5.0 million and her hemoglobin 90 per cent.

At this time one of us (J. H. M.) made a note to the effect that she undoubtedly had exophthalmic goiter and that this appeared to have followed the development of a state of malnutrition, also that although her thyrotoxicosis was mild she was a poor risk for surgery on at least three counts: (1) because she had the complication of chronic rheumatic heart disease; (2) a very unstable psyche; and (3) a very severe grade of malnutrition.

She was given iodine and made a good response as far as symptoms went and her basal metabolic rate dropped to a normal level. Instead of operating at this point, however, it was felt wiser to send her home on iodine and high calory, high vitamin diet. She was given vitamin B in the form of Harris Yeast Tablets.

On March 19, 1936, she reëntered, having gained seven pounds and become less nervous. A subtotal thyroidectomy was done on March 27, which she went through uneventfully and on April 4 her basal metabolic rate was minus 1.

She did well for about eight months, but then developed a mild recurrence of thyrotoxicosis which threw her heart into fibrillation. Iodine controlled the thyrotoxicosis adequately, but the fibrillation continued. In January of 1937 she went through a sharp attack of bronchopneumonia without thyrotoxic exacerbation or gross cardiac decompensation. Although it cannot be proved, our guess is that her course through thyroidectomy would have been far less smooth if she had been operated upon immediately after the establishment of iodinization.

In conclusion, we should like to warn physicians and patients against too vigorous reduction cures for obesity; thyrotoxicosis may be induced thereby; and in the preparation of the thyrotoxic patient for operation we should like to urge that the possibility of nutritional disturbances be considered and, if found, that an attempt be made to correct them.

The manifestations of nutritional disturbance, which may be found in thyrotoxic patients, include, as well as general inanition, changes in musculature, skeleton, hematopoietic system and very likely in the heart and psyche. While these findings may be merely incidental and their causal relationship to thyrotoxicosis ascertainable only by an extensive statistical study, we feel that they are of sufficient frequency to warrant consideration in the complete management of patients ill with Graves' disease.

The methods of correcting these defects include not only a high calory diet for relieving general malnutrition, but one high in vitamins and minerals as well. Vitamin B_1 may be of special significance as having appetite increasing proclivities, and also perhaps some special beneficial action upon cardiac function. We are now using Harris Yeast Tablets for this purpose. Pure vitamin B_1 preparations can be used when the indication seems urgent.

For the high calory intake the chief dependence should be placed upon carbohydrate. Excessive protein is undesirable because through its specific dynamic action protein raises metabolism. Carbohydrate, on the other hand, in large amounts is insurance against depletion of the glycogen stores of the liver and thus safeguards that organ. With regard to fat, there is no special indication that we know of. Fat may be given to whatever extent the patient's appetite demands.

We feel that there is good reason for regarding the malnourished thyrotoxic patients and the psychotic as well as those with cardiac insufficiency as poor operative risks. It is wise to get their weight curves at least started upward before permitting operation. This sometimes will require several weeks of pre-operative medical treatment. There is a tendency to rush thyrotoxic patients too fast to the surgeon. It is the physician's responsibility to see that this be not done. It is also his responsibility to avoid unnecessary delay in the securing of relief of thyrotoxicosis by operative intervention. Although it is desirable that he have certain definite routine procedures—the use of iodine, for example—it is also desirable that he study

each case as an individual problem and plan his actual therapeutic program to meet individual indications.

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A STUDY OF THE DIAGNOSIS AND TREATMENT OF LOBAR PNEUMONIA ACCORDING TO TYPES AND SPECIFIC SERUM THERAPY *

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ALTHOUGH recent reports of successes in the diagnosis and treatment of the pneumonias, according to specific criteria, have been impressive, it can hardly be said that the medical world is committed to the procedures. There are several valid reasons why this is true. While there have been excellent results reported by reliable observers in the treatment of the acute pneumonias with specific serum, the technical difficulties involved in accurate typing, as well as the expense incurred in the use of curative serum, are the major objections raised, and the ones which have caused clinicians to approach the subject with hesitation. These two obstacles will be overcome only when public health facilities are more widely distributed, so that laboratories, where typing may be done day or night, are more conveniently located; also funds must be made available for the purchase of curative serum, so that rich and poor alike may have its advantages. At present this is not true even of all cities of major size, to say nothing of the rural districts. Another possible reason why serum has not been more generally employed in the treatment of pneumonia is because of the doubts as to its efficacy, which many clinicians still harbor. In many instances the reasons for their scepticism appear well founded, and they will be won over only when serum therapy has arrived at the stage of infallibility.

The technic incident to correct, accurate, and rapid typing by the Neufeld method has been represented by enthusiasts as being an essentially simple technic, capable of accomplishment in any physician's office where technical assistance exists. It is quite possible that this explains some of the disappointments experienced by many reliable clinicians who have attempted the procedure. There is one thing that stands out with great certainty, namely, that if typing is not reliably done, the results in the administration of serum are bound to be disappointing. Whereas in a majority of instances the Neufeld technic is accomplished with little or no difficulty, in a certain percentage of cases difficulties will be encountered, necessitating arduous and painstaking study as well as special technical skill for their correct solution. When organisms are few in number, media suitable for the growth of pneumococci must be available (Avery broth or mice) so that the technician may find the invading organism which might otherwise be missed. Complete typing should also be instituted routinely, as in many instances two or even three types of pneumococci may be found in the same sputum. This infor-

* Read at the St. Louis meeting of the American College of Physicians, April 21, 1937.

mation while puzzling at times, is of aid in the prognosis as well as diagnosis. Only in laboratories equipped with facilities not only for direct typing, but also for the transplanting of cultures to mice and broth media, are satisfactory reports obtained.

While it is true that lives have been saved by the administration of serum at any time during the course of the disease, the greatest saving of lives occurs in those individuals who are fortunate enough to contract a type of pneumonia for which curative serum is available, and who are treated shortly after the inception of the disease. It should be possible, in the not too distant future, through a process of health education, to arouse public interest to the necessity of calling for medical aid early in the course of severe, acute respiratory disease. For the present, at least, this is not true and we are forced to treat situations as they exist. Furthermore, the disease unfortunately attacks in largest numbers those of the laboring class, and of these, the majority live under adverse conditions. Quite naturally, medical aid is not sought so early by this large group as by those in the higher economic level, where the disease is far less common. Practically all of the reported data concerning the specific treatment of the pneumonias have emanated from medical centers or large public hospitals. Had it been necessary to rely on the statistics gathered from private hospitals, or in private practice, advances in this important aspect of the disease would have been much slower.

Those who have been closely associated with this method must admit that it represents the greatest advance in the control of this deadly disease, which has been made since pneumonia was first described.

Under the careful directions of such well known clinicians as Bullowa, Finland, Cecil and others, the mortality rate for the early treated cases of the commoner and more frequent types of pneumonia has been reduced as much as 50 per cent of its former high figure. In the more malignant types, and in the late cases the mortality rates have also been appreciably reduced. It was possible at the Cincinnati General Hospital in the year 1935 to 1936 to report the first series of 50 consecutive cases of Type I pneumonia treated within 96 hours of onset, without a single death.[1] These results were accomplished under anything but perfect conditions. The patients were inadequately nursed, the wards were considerably overcrowded, the patients were of the indigent class, many of them alcoholics. There was at hand, however, the setup for excellent laboratory work, and the enthusiasm for prompt and unrelenting administration of serum. We are now in our third year of study of the lobar pneumonias, according to this method. It is a critical analysis of some of our observations during the past 16 months which forms the basis of this discussion.

There are included in this study only the lobar pneumonias, with but few exceptions, occurring in adults. It is primarily intended as a critical appraisal of the beneficial effects of concentrated specific, curative serum in

patients whose pneumonic symptoms have existed 96 hours or less.* The treatment was instituted on the basis of Neufeld typing of sputum, mouse transplants and broth cultures. Commercial sera † for Types I, II, V, VII and VIII were used. There was also available, through the generous offer of the Littauer Pneumonia Fund, Harlem Hospital, New York City, serum for Types VI, XIV and XVIII. Blood cultures were taken in each instance, repeated when indicated, and the colony count followed.

The incidence of lobar pneumonia is quite high in Cincinnati. Morbidity rates are practically impossible to obtain, but each year there are more than 300 deaths attributed to this type of the disease, representing a mortality of 75.3 per 100,000 population. For the 16 months, October 1, 1935 to February 1, 1937, there were received at the Cincinnati General Hospital 485 cases. (Table 1.)

TABLE I

Cincinnati General Hospital
Incidence of Color, Sex, and Death Rates in Lobar Pneumonia
October 1, 1935 to February 1, 1937

	No. of Cases	Deaths	Per Cent
White	245	60	24.53
Colored	240	62	25.83
Males	344	79	22.96
Females	141	43	30.49
Total	485	122	25.15

Almost an equal number of white and colored patients were examined and treated, and they died in about the same proportion. There was a crude mortality rate of 25 per cent as against a crude rate of 30 to 50 per cent over a period of six years, studied by Schiff [2] prior to the general use of type specific serum.

The distribution of cases according to age groups is shown in table 2. It is noteworthy that although only 42 per cent of the total number appeared after the fourth decade, 67 per cent of the deaths occurred during those years.

* The time interval of 96 hours has been arbitrarily selected, because of the possibility of a spontaneous crisis occurring after that time. Our criteria for establishing the diagnosis of lobar pneumonia have been:

1. Typical acute cases (early).
   (*a*) Sudden onset—chill, pain, fever, cough, rusty sputum.
   (*b*) Typing of sputum.
2. Atypical and late cases.
   (*a*) History upper respiratory infection with sudden change as under (*a*) above.
   (*b*) Physical examination indicating consolidation.
   (*c*) Typing of sputum.
   (*d*) Roentgen-ray in all doubtful cases.

In each instance, the subsequent findings on physical examination were always relied on as corroborative evidence of the existence of pneumonic consolidation. Further, more than one clinician examined each patient.

† One kind of serum was used throughout the investigation.

TABLE II

Cincinnati General Hospital
Incidence of Age and Death Rates in Lobar Pneumonia
October 1, 1935 to February 1, 1937

Decade	Number of cases	Percentage of incidence	Number of deaths	Percentage of total deaths	Percentage of deaths by decade
0–9	9	1.9	1	0.8	11.1
10–19	50	10.3	4	3.3	8.0
20–29	114	23.5	14	11.5	12.3
30–39	104	21.0	22	18.0	21.5
40–49	96	19.8	36	29.5	37.5
50–59	58	12.0	23	18.9	39.7
60–69	40	8.3	14	11.5	35.0
70–79	13	2.6	7	5.7	53.8
80–	1	0.3	1	0.8	100.0
Total	485		122		

In table 3 the cases are grouped according to serological types. Type I, the so-called "typical pneumonia," was responsible for 32 per cent of the entire group. Adding to this number, those other cases of the types for which curative serum exists (I, II, V, VII, and VIII), brings out the fact that for 66 per cent of the patients in this series appropriate curative serum was available.

Since only early cases were treated energetically with serum, a very considerable number of these patients did not receive this form of treatment. Of interest, however, are the results of serum treatment in some of these types.

We have worked on the thesis that there is no arbitrary dosage of serum in pneumonia, since so many factors must be evaluated in the treatment of the individual case. We have, however, set a certain minimal standard or range of dosage for each of the treatable types. These are Type I, 60–80,000 units; Type II, 100–120,000 units; Type V, 80–100,000; Type VII, 60–80,000 units; and Type VIII, 60–80,000 units. All of the "treated" patients received at least these amounts of serum intravenously. The initial dose consisted usually of 20,000 units, although in some cases it was only 10,000. The remainder of the minimal standard dosage was given at two hour intervals, each subsequent dose varying from 40,000 to 80,000 units. If blood cultures proved to be positive, from 60,000 to 100,000 additional units were administered, provided that the desired clinical effect had not intervened meanwhile.

Type I. It has been shown conclusively that specific serum reduces the mortality in pneumonia due to Type I pneumococcus.[1, 3] While this is of the greatest importance, it is not the only criterion of the efficacy of serum. It is of equal interest to observe the effect of serum on the course of the disease in each patient. The uniformity with which rapid clinical improvement may be correlated with the administration of serum is of help, not only

TABLE III

Cincinnati General Hospital

Incidence of Types and Deaths in Lobar Pneumonia
October 1, 1935 to February 1, 1937

Type	No. of Cases	Deaths
I	156 (32%)	25
II	52 (11%)	17
III	50 (10%)	28
IV	20 (4%)	1
V	47 (9%)	13
VI	9	2
VII	43 (8%)	6
VIII	30 (6%)	3
IX	8	1
X	2	0
XI	1	1
XII	13	4
XIII		
XIV	6	3
XV	1	0
XVI		
XVII		
XVIII	6	1
XIX	10	4
XX		
XXI		
XXII	2	0
XXIII	1	0
XXIV		
XXV	12	5
XXVII		
XXVIII	2	1
XXIX	1	1
XXXI		
XXXII		
Unclassified	12	6
Total	485	122
Crude mortality		25.15%

in evaluating the efficacy of this agent, but also in defining the limits of its usefulness. Therefore, these criteria will be briefly discussed.

In table 4 a comparison of serum treated and non-serum treated cases is shown. The reduction in the death rate was striking. The crude mortality holds for different seasons, according to age, sex, and the presence or absence of bacteremia, and with respect to the extent of the pulmonary lesion. Our series shows that the mortality rate for all types not treated with serum amounted to 31.5 per cent. It is also apparent that contrary to popular belief, Type I pneumonia is not a relatively mild type of infection, since in our series the mortality rate for the untreated cases was 26.5 per cent. The early serum treated cases of Type I had a mortality rate of only 4.11 per cent.

The effect of the serum on the course of the disease is no less impressive. Almost all of the patients favorably affected were much more comfortable within two to three hours after serum administration, and crisis was com-

plete or nearly so within 24 to 36 hours. While actual crisis was observed as frequently in the untreated patients who survived, undoubtedly its onset was materially hastened in those receiving serum. Examining for a moment those cases of Type I considered therapeutic failures, the following facts are revealed.

TABLE IV

Cincinnati General Hospital
Comparative Mortality in Serum and Non-Serum Treated Cases
October 1, 1935 to February 1, 1937

	Serum Treated within 96 hrs.			Others *		
Type	No. of Cases	Deaths	Death Rate	No. of Cases	Deaths	Death Rate
I	73	3	4.1%	83	22	26.5%
II	26	8	30.7%	26	9	34.6%
V	11	2	18.1%	36	11	30.5%
VII	18	0		25	6	24.0%
VIII	8	0		22	3	13.6%
†XIV	2	0		4	3	75.0%
†XVIII	1	0		5	1	20.0%
Total	139	13	9.3%	201	55	27.3%

* A few of these patients received some serum, late in the disease, for experimental purposes.
† Obtained through the courtesy of the Littauer Pneumonia Fund, Harlem Hospital, New York City (Dr. Jesse G. M. Bullowa).

Case 1. White, male, aged 78, admitted on the fourth day of the disease, with consolidation involving the right upper lobe. There was a history of previous coronary thrombosis, and evidence of auricular fibrillation. Marked nitrogen retention. White count 3,200 and later 1,900. Bacteremia of high degree. Died same day serum was given. He received 100,000 units.

Case 2. White, male, aged 65, admitted to the hospital with delirium tremens, and supposedly developed lobar pneumonia in the hospital. Leukocyte count 7,900. This man died with symptoms and signs of acute cardiac failure. There was also a question of beri-beri. He probably had had pneumonia longer than estimated. His death occurred on the same day that serum (118,000 units) was given. Necropsy revealed extensive empyema.

Case 3. White, male, aged 49. Second day of the disease. Blood culture positive after 100,000 units. Leukocyte count 6,500. He died the day after serum therapy. Doubtless, this patient should have received more serum.

The first two cases probably represent the irreducible minimum, since a certain number of derelicts and patients with severe degenerative diseases will inevitably succumb to the ravages of pneumonia, as the precipitating cause of their demise.

Whether or not a simpler and less drastic method of introducing antibody is suggested in years to come, we now have at our command a most reliable, specific, therapeutic agent to combat effectively that type of pneumonia which affects by far the largest number of people.

Other Types. There is ample proof that specific serum is a reliable therapeutic agent in several other types besides type I. Certain features in

some of the types present minor difficulties, which have not been entirely obviated. In addition, the remaining 31 types, although their distribution is uneven, do not concentrate in any type in sufficiently large numbers to permit of reliable analysis. Caution must be observed in making deductions in so important a subject, with a relatively small number of cases. With this in mind, instead of subjecting each of the Types II, V, VII, VIII, XIV and XVIII * (the only other ones for which therapeutic serum is available) to critical analysis at this time, it is of interest to consider the results obtained in these types considered together. Table 4 is valuable in this respect since it illustrates the saving in lives, possible with this treatment. The numbers are sufficiently large to be significant. It is noteworthy that the mortality is three times as great in those patients who were not serum treated, as in those receiving serum.

Type II pneumonia is for us a difficult problem. Data at hand, gathered from the study of 52 cases, indicate a comparable death rate of 30 and 34 per cent respectively, in cases treated specifically and non-specifically. In the final analysis it appears that in each unsuccessfully treated case, insufficient quantities of serum were given. The dose of serum for this type may ultimately be found to be three or more times the amount required for other types. In Finland's experience 200–300,000 units were necessary.[4]

Type V, it will be recalled, was the original Avery Type IIa. Nine per cent of our series fell into this type, a total of 47 cases. Of this number 36 were seen later than 96 hours after onset of their illness. None of these received serum and 11 of them died (30.5 per cent). Of 11 patients treated with serum earlier than 96 hours, only 2 died (18 per cent). Thus Type V is a pneumonia of high virulence when neglected, and quite amenable to specific therapy.

Type VII is often a fairly severe type of pneumonia which yields quite satisfactorily to serum administration. It is almost as prevalent as Type V. Of 18 consecutive cases treated early, not one succumbed, as against 6 deaths in 25 untreated cases (24 per cent).

Type VIII, related immunologically to Type III, is likewise favorably affected by serum therapy as far as anyone may judge from a small number of cases (30). No deaths occurred in the eight cases treated within 96 hours of the onset of pneumonia; there were three deaths among the 22 cases treated symptomatically. This type of the disease is, generally speaking, of the mild kind, if there be such in pneumonia, since the mortality rate was only 13 per cent for patients receiving no serum.

Bacteremia. The importance of determining whether or not a blood stream infection is present, early in the course of pneumonia, cannot be overemphasized. No single factor influences the outcome so directly. The death rate in patients having bacteremia is exceedingly high. While the numbers here presented are not large, owing to the fact that we have taken

* Obtained through the courtesy of the Littauer Pneumonia Fund, Harlem Hosp., New York City. Dr. Jesse G. M. Bullowa rendered this and other valued help.

TABLE V

Influence of Bacteremia

Type	Cases with *Positive* Blood Culture		Cases with *Negative* Blood Culture	
	Number	Deaths	Number	Deaths
I	11^{5}	9^{3}	29^{15}	1
II	11^{4}	8^{3}	19^{14}	3^{3}
III	10	10	23	5
V	7^{2}	4^{1}	7^{2}	0
VII	4^{3}	0	18^{8}	1
VIII	6^{3}	2	9^{1}	1
Total	49^{17}	33^{7}	105^{41}	11^{3}

Superscript represents serum treated cases within 96 hrs.

Death Rate—Cases with positive blood culture	67.3%
Cases with negative blood culture	10.4%
Serum treated cases with pos. Bl. Cl.	41.1%
Non-Serum treated cases with pos. Bl. Cl.	81.0%
Serum treated cases with neg. Bl. Cl.	7.3%
Non-Serum treated cases with neg. Bl. Cl.	12.3%

blood cultures routinely only since October 1, 1936, it is noteworthy that of 49 patients with positive blood cultures who did not receive serum, 81 per cent died. On the other hand of 17 patients with bacteremia who received serum within 96 hours of the onset of their illness, 41 per cent died. Undoubtedly this percentage is susceptible to considerable further reduction. We believe that such cases require two to three times the quantity of serum ordinarily administered. Further, the treatment must be continued until the blood is sterile. The importance of blood culture determination early in the disease is only second to correct typing of sputum, the one to determine specific diagnosis, the other as a guide to dosage of serum.

There is abundant evidence also that complications are related to the presence of bacteremia. During the past six months we have studied more intensively the influence of blood stream infection on the general course of the disease. In reviewing the commoner complications of the pneumonias for the period October 1936 to February 1937 the data obtained (table 6)

TABLE VI

Complications
October 1, 1936–February 1, 1937

	Bacteremic	Non-Bacteremic
Empyema	8	2
Meningitis	5	1
Endocarditis	4	0
Pyarthrosis	2	0
Pericarditis	1	1
Lung Abscess	1	2
Pleural Effusion	0	4
Otitis Media	6	0
Thrombo Phlebitis	0	1
Total	21	12

indicate in an interesting manner that the serious complications (empyema-meningitis-endocarditis) occur more frequently in the bacteremic cases.

Discussion of Serum Therapy

The importance of giving adequate amounts of serum relentlessly until definite signs of improvement appear, cannot be overemphasized. The introduction into the blood stream of foreign protein in such quantities has produced very few unfavorable reactions. Indeed we have been amazed at the negligible number of thermal reactions and instances of serum sickness. This was doubtless due to the fact that the new concentrated and highly purified therapeutic serum was used. In all we observed 23 cases of serum sickness, and 19 cases which showed immediate reactions to serum, 8 slight, 9 moderate, and 2 severe. In one instance of a severe reaction, the use of serum was possibly contraindicated by a mildly positive skin test to horse serum.

In almost all favorable cases, very soon after the administration of serum, the patient's general condition improves. The cyanosis becomes less, the pulse rate usually falls and respiration appears less arduous. Then follows gradually a lowering of temperature, amelioration of other symptoms and within a few days the patient returns to a normal condition. What is equally important is that there is rarely extension of the lung lesion. The detoxifying effect of serum is frequently prompt and startling. Further, its sterilizing effect on bacteremia is worthy of note.

Effect on Resolution. While the administration of serum causes no change in the rate of resolution of affected lung tissues, there is no evidence that this process is interfered with, or delayed. Certainly those individuals successfully treated remain in the hospital for a much shorter time than those non-serum treated. The days of intense suffering are also materially reduced.

Effect on Mortality. The final test of the effectiveness of immune serum must rest on the evidence concerning the saving of lives. While the studies reported herewith do not represent a very large number of cases, the results compare most favorably with those reported by other observers. Undoubtedly the saving in lives is greatest in Type I infections; but in the other types as well the lowering of mortality rates of serum treated cases as against non-serum treated cases, is definite. It is not too radical to conclude that "no patient with Type I infection who dies without the early intravenous administration of large doses of Type I serum, can be said to have received the best treatment."[5] There is abundant evidence that potent immune serum exists for types which together comprise 65 per cent of all lobar pneumonia. It is hardly adequate medical treatment if so many lives continue to be needlessly sacrificed.

According to Rogers,[1] there occur, annually in Ohio, in the vicinity of 3,000 deaths from lobar pneumonia, indicating about 12,000 cases. About

96 per cent of all cases of " lobar pneumonia " are pneumococcal in origin. Of the 12,000 cases 65 per cent, or 7,800 cases, may be assumed to be due to Type I, II, V, VII, or VIII. On the basis of our knowledge of the potential effect of serum, we find that 1,400 lives might be saved, a reduction of 46 per cent in the mortality from this disease. Although it is improbable for a variety of reasons that this goal can be attained in the near future, nevertheless we should be urged on by the fact that there exist today, therapeutic agents which make this achievement possible.

The difficulties in our path are largely those of lay education and public health organization. It is gratifying to note that the states of New York, Massachusetts, Connecticut and Michigan are now well organized in their approach to the prevention and specific treatment of the pneumonias. Facilities for prompt typing of sputum as well as appropriations for the purchase of serum for the indigent, exist as an important plank in their campaigns against preventable and curable diseases. While only specific serum for Type I and II is usually available, one of the states has already increased its funds so as to include Types V, VII, and VIII.

This represents a progressive attitude on the part of public health officials. Undoubtedly great reduction in pneumonia mortality will be the result of their efforts. The educational pamphlets distributed to the public and profession by these officials will go far toward rounding out their program of prevention.

That the pneumonias in a large percentage of instances are readily communicable from one individual to another is an accepted fact. For this reason, the enforcement of the same precautions as are taken in the effort to control the spread of other contagious disease is justifiable. Compulsory notification should be instituted without delay. Each case of pneumonia should be regarded as a focus for the spread of the infection, and the care of each patient should include those measures which have been found serviceable in other communicable diseases. We were convinced of the need of segregating patients in cubicles rather than treating them in the open ward and of requiring physicians and nurses to observe the same precautions in caring for these patients as are usual in contagious disease wards. The wearing of gowns and masks and washing hands after each examination or treatment should be strictly enforced. Before instituting these procedures, not a few instances of cross infection occurred in our ward. The type of pneumonia contracted was frequently traceable to patients in nearby beds. There were also encountered cases in individuals who had visited pneumonia patients in the hospital. We have likewise records of two or more members of a family contracting pneumonia of the same type in succession. Recently Finland and Tilghman [6] emphasized this fact and in their conclusions stated that bacteriologic studies made on members of households in which multiple cases of pneumococcus infection were observed, revealed a high incidence of carriers of the type of pneumococcus responsible for the infections in the relatives.

Conclusions

1. Of 485 typed cases of lobar pneumonia observed during a 16 month interval, 66 per cent fall within those types for which therapeutic serum is available.

2. Early diagnosis of the exact etiological agent of lobar pneumonia is of paramount importance in serum therapy; blood cultures are necessary, frequently as diagnostic procedures, and always for prognosis.

3. In comparable series of Type I patients, the mortality among those receiving serum within 96 hours of the onset of the disease was 4.1 per cent whereas 26.5 per cent of the non-serum treated patients died. In much smaller groups of patients similarly striking results were shown after the use of specific serum in Type VII and Type VIII pneumonia respectively.

4. Specific serum treatment of all patients (Types I, II, V, VII, VIII, XIV and XVIII) seen within 96 hours of onset, resulted in a death rate of 9.3 per cent. Of the group not treated with a specific serum 27 per cent died.

5. Bacteremia influences the prognosis unfavorably and is an indication for the administration of larger quantities of serum.

6. The intravenous administration of refined, concentrated antipneumococcus horse serum is not fraught with severe, untoward reactions in the non-sensitive patient.

7. Lobar pneumonia is a contagious disease and as such should be treated as a public health problem.

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SOME CLINICAL CAPRICES OF HODGKIN'S DISEASE *

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In 1856 Samuel Wilks [1] wrote, " It is only to be lamented that Dr. Hodgkin did not affix a distinct name to the disease, for by so doing I should not have experienced so long an ignorance (which I believe I share with many others) of a very remarkable class of cases, a recognition of which would have guided both myself and others to an explanation of some more recent instances coming under our notice." Nine years later Wilks [2] critically analyzed Hodgkin's materials [3] and found that the latter had included other pathologic conditions than the one bearing his name through the magnanimous gesture of the former. An interesting confirmation of this position was afforded by Fox's reëxamination of the original tissues [4] after an interval of 97 years from the time of their preservation.

If confusion marked the histologic definition of Hodgkin's disease, its clinical delineation could scarcely be expected to escape similar difficulties. Eventually there have been evolved diagnostic criteria and clinical features that typify the classical case. Briefly stated, Hodgkin's disease occurs characteristically in the age period between 18 and 35 years with a predilection for the male sex in the proportion of two to one. Two secondary and minor peaks are observed in the incidence curves, namely between five and ten years for both sexes and at the menopause for women. Insidiously the lymph nodes of a single group, as the posterior cervical chain, become involved in a singular manner. They are painless and non-sensitive unless a nerve trunk be involved. Their firmness varies with the cellular content, supporting framework and capsular tension. As a rule it approximates the consistency of cartilage. Until late in the course of the untreated subject the affected nodes remain discrete and unattached to the overlying or the underlying structures. Redness and increased temperature of the skin are rarely observed over the involved nodes. Suppuration is very unusual. In the cervical involvement eventually a characteristic pyramidal conformation results with the largest nodes at the base above the clavicle and the smallest ones in the apex at the angle of the jaw.[5] Eventually the process becomes bilateral, involves the lymphoid system widely through the body and includes the liver and the spleen in its pathologic changes. In general the involvement of the lymphoid tissues of the body is progressive but marked remissions with reduction in their bulk may occur spontaneously from time to time.

The local symptoms of Hodgkin's disease will depend on the site of the lymphadenopathy. They may include among other manifestations, paresthesias and pain from neural pressure, Horner's syndrome from sympathetic destruction, cyanosis and edema from interference with venous return

* Read at the St. Louis meeting of the American College of Physicians, April 21, 1937.
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(lymph stasis contributing), dyspnea, cough, superior cyanosis and dysphagia from mediastinal involvement. Jaundice may result from common duct obstruction through lymphadenopathy or from direct invasion of the liver by the cellular reaction of the disease. Splenomegaly is a common manifestation and its degree may induce independent symptoms of dragging discomfort, early satiety and constipation. Hepatomegaly may lead to right-sided abdominal pain. Certain skin manifestations are encountered. Among these, brownish pigmentation and intractable pruritus take prominent places. A wide diversity of symptoms may result from the involvement of other organs or tissues.

The constitutional reactions of Hodgkin's disease are extremely variable. Fever occurs at some time in the course of practically all cases. In some it appears early and remains a prominent detail of the composite clinical picture. In others its appearance may be deferred to constitute a serious portent. Its form likewise is variable. Remittent fever is the rule but occasionally a continuous type is encountered. Finally there is a singular form of fever in this disease that is designated by the names of its several observers, Murchison,[6] or Pel[7]-Ebstein.[8] Such a fever is marked by bouts of remittent or continuous pyrexia and intermissions of apyrexia. Chills and sweats of varying degrees may attend the fever. While classically a remarkable regularity in the time and the degree of the febrile episodes as well as in the duration of the afebrile intervals may be anticipated, any recurring fever may assume a diagnostic significance in the presence of other clinical evidences of Hodgkin's disease. Tachycardia may occur independently, but usually parallels the febrile course. Cachexia appears sooner or later in most patients with Hodgkin's disease unless serious obstructive symptoms unduly shorten the course. Furthermore pallor and wasting are grave prognostic details.

The laboratory findings include the blood picture so adequately discussed by Bunting.[9, 10] Beyond a question of doubt in the hands of expert hematologists his criteria offer a differential diagnostic aid of great usefulness in the presence of progressive lymph node involvement; but in the wider sense the transition from an early phase of lymphoid resistance to a late one of lymphoid paralysis affords a prognostic index of surpassing utility provided the blood has been followed consecutively with other clinical observations. An anemia of the hypochromic type is the rule and it may assume profound degrees. The platelets are increased in virtually all cases. The basal metabolic rate is elevated during the periods of clinical activity of Hodgkin's disease[11]; but there is apparently no diagnostic implication in this observation. The ultimate diagnosis may in many cases rest upon the histologic examination of the affected lymph node. Certainly Gordon's studies upon the central nervous changes incident to the intracerebral and intravenous injections of emulsified lymph nodes[12] offer no material diagnostic assistance. The high incidence of mediastinal involvement[13] indi-

cates the advisability of roentgenoscopy and roentgenography in the investigation of this field. Likewise roentgenograms of other suspected areas, as the bony framework, gastrointestinal system and so forth, may extend the clinical prospect.

Few clinical conditions conform more closely to the accepted descriptions than does the typical case of Hodgkin's disease. At the same time there is no disease with a more diversified range of clinical expression. On one hand these variants may result from the overwhelmingly predominant emphasis upon some common or uncommon feature of the disease. Again some clinical vagary may so distort the picture as to render its diagnosis extremely difficult.

With this thought in mind a series of such instances of Hodgkin's disease has been briefly digested:

I. Age

Case 1. A white female, aged 6, complained chiefly of coughing. This cough had persisted for five months without expectoration. There had been no weight loss but progressive weakness had been observed and breathing had become somewhat difficult. Two months after the onset and concurrent with an apparent respiratory infection, enlargement at the base of the neck on the left side was observed.

The physical examination established the presence of firm, movable supraclavicular nodes on the left with dullness and bronchial breath sounds in the upper left chest. Below this, anteriorly, the breath sounds were absent but posteriorly the breath sounds were within normal range. The blood count was significant only in the polymorphonuclear neutrophilia of 87 per cent of a total leukocyte count of 8,150. Roentgenogram of the chest showed a mediastinal mass with extension to the left. Two months after the first admission, the patient was reëxamined and at this time fluid had appeared in the left thoracic cavity, and it proved to be serosanguinous upon aspiration.

Case 2. A white male, aged 84, entered with a chief complaint of "tumor of the neck," which condition was dated to a sore throat four years previously when a small purplish tumor was observed in the right tonsil. The occurrence of lymph node enlargement in the right side of the neck led to radium treatment of the tumor of the tonsil and surgical removal of the cervical masses. A year and a half later tumors recurred in the right side of the neck and later the left side was likewise affected. These progressed slowly and were removed surgically. Following their extirpation, roentgen-ray treatment was renewed, but after its discontinuance the tumors reappeared slowly and painlessly. The general health remained unimpaired and there was slight weight loss.

The physical examination was significant only in the definition of the cervical lymphadenopathy involving the submaxillary and the anterior and posterior cervical chains. These nodes were firm in consistency and irregular in shape. There was apparent attachment to the underlying structures but none to the overlying skin.

By reason of the extremes of age in Cases 1 and 2, six and 84 years respectively, Hodgkin's disease had not been a primary consideration and only upon biopsy was such a diagnosis possible.

II. Skin Manifestations

A. Pruritus

Case 3. A white male, aged 28, complained of shortness of breath. His trouble was dated to eight months ago when a troublesome itching developed over the entire body. Six weeks later a respiratory infection supervened and there was a relapse a week after its onset, so that the patient remained in bed for a week and a half. Following this, weakness persisted and vomiting became intractable. Four months after the onset, he went to the Rocky Mountains for a rest and fluid was found in the left pleural cavity. After an aspiration, the diagnosis of Hodgkin's disease was made by the biopsy of a cervical lymph node. The succeeding course was one of recurrent accumulation of fluid in the pleural cavity with progressive loss of ground.

The skin was particularly interesting in the encrusted, excoriated areas over the back and legs and the scarring and pigmentation at the site of old lesions. Lymphadenopathy of a characteristic order, splenomegaly and hepatomegaly with the evidence of mediastinal involvement ultimately completed the picture.

Pruritus is a well recognized manifestation of Hodgkin's disease. Not infrequently it succeeds other and more clearly defined evidences of the condition, but occasionally as in Case 3 pruritus may anticipate the characteristic lymphoid changes by a considerable period.

B. Ulceration

Case 4. A white female, aged 26, experienced considerable difficulty in the healing of a wound subsequent to a biopsy in the left axilla three and a half years before admission. This study confirmed the diagnosis of Hodgkin's disease but subsequently cervical lymphadenopathy appeared and the characteristic pyramid of discrete, nontender lymph nodes was noted. Extended roentgen-ray treatment was thereafter applied in both cervical and the left axillary regions. The left breast became involved and extension from the original site was suspected. With slight fluctuations the process was well controlled by roentgen-therapy; but in the intervals between treatment, sharp accessions in the process occurred in the above described areas. Twenty-seven months after the first observation in this hospital, the patient noticed a draining sinus in the right upper chest and there was progressive enlargement of the involved lymph nodes. Three subsequent admissions over the following 14 months showed some extension of the ulceration in the right infraclavicular region. This ulceration had a gray, dirty base with abrupt margins. A second supraclavicular sinus appeared. Eventually these two areas joined to form a single ulcer 10 by 12.5 cm. and the edges showed slight sluggish granulation.

Suppuration of the lymph nodes in Hodgkin's disease with resultant sinuses is unusual. Indolent ulcers on this basis are even rarer. Just what part roentgen-therapy played in the sequence of events in Case 4 is impossible to state. Unfortunately the earlier experience of the patient led her to refuse a biopsy of the margin and the base of the ulcer that might well have fixed the etiologic responsibility.

C. Breast

Case 5. A white female, aged 58, complained of a lump in the breast which had been noted for a year. At first there had been a small lump the size of a hickory nut in the right axilla and this had grown to such an extent six months previously

that she consulted a physician who advised amputation of the breast. The size of the mass alone inconvenienced the patient.

Through careful examination it became apparent the mass had arisen in the right axilla as stated by the patient and extended beyond the anterior axilla leading into the upper and outer segment of the breast and lying superficially to the pectoralis major. Posteriorly the mass extended across the axillary line to elevate the skin over the latissimus dorsi. It did not involve the apex of the axilla. In consistency it was firm but not of stony hardness. It was not attached to the skin nor to the deeper tissues. It was nontender and there was no general lymphadenopathy (figure 1).

Under general anesthesia the mass in the right axilla was resected and proved to be Hodgkin's disease.

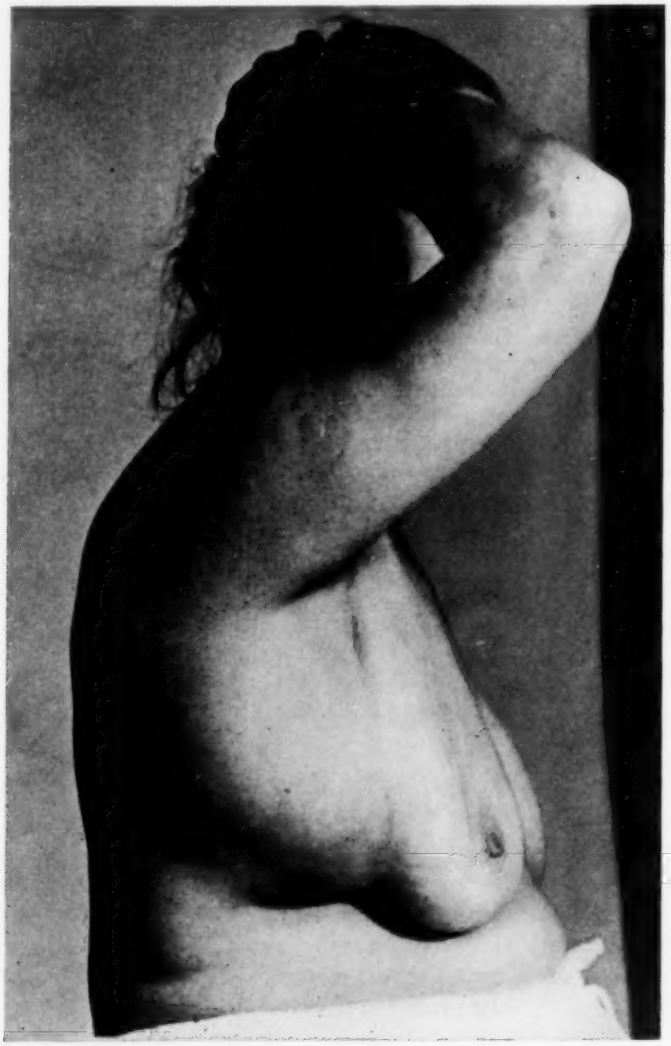

FIG. 1. Hodgkin's disease of the axillary lymph nodes erroneously diagnosed tumor of the breast (Case 5).

Particular interest attaches to Case 5 by reason of the mistaken diagnosis of a tumor of the breast, whereas an accurate history supported by a careful physical examination clearly traced the mass to its original site in the right axilla.

III. Neural Involvement

A. Neuritis

Case 6. A white male, aged 36, complained of pain in the right leg. For eight to ten weeks prior to admission the patient had experienced a constant dull ache in the calf of the right leg which made it impossible for him to straighten the leg. Shooting pains into the hip and thence down to the ankle on the posterior aspect of the leg had been experienced from the onset. These occurred chiefly in the night when the patient was in bed and lasted from 15 to 30 minutes. Heat and counter-irritants relieved the pain at first but later had no effect. More recently heat with massage seemed to give more relief. These pains had increased in severity and frequency, particularly in the week immediately preceding admission, until they had become practically continuous at the time of admission. Excessive sweating especially along the back had appeared.

There had been an appendectomy three months previously and at this time an intraabdominal mass had been determined. A cough had continued from the time of the operation and the mucus produced was occasionally blood streaked.

To physical examination pallor was evident. A few small, discrete, firm anterior and posterior cervical lymph nodes were noted. The axillary and epitrochlear lymph nodes were barely palpable. The spleen and liver were felt. There was also marked tenderness in the course of the right great sciatic nerve. A biopsy confirmed the diagnosis of Hodgkin's disease. The course was progressively downward during the hospital stay of 63 days, during which period the patient ran a widely remittent temperature, ranging from 99 to 104.8° F.

The blood picture was particularly interesting in that a terminal level of 24 per cent hemoglobin, 1,530,000 erythrocytes, 600 leukocytes, with 53 per cent neutrophiles, 1 per cent eosinophiles, 45 per cent lymphocytes and 1 per cent mononuclears was obtained the day before death.

The suffering of this patient from sciatic neuritis was extreme. The clear intimation of a neoplastic background lay in the determination of an intraabdominal mass at the time of the appendectomy. Hemoptysis, remittent fever, grave anemia and profound leukopenia completed the clinical picture in this subject.

B. Herpes Zoster

Case 7. A white male, aged 40, complained of a lump in the neck. He stated that twelve years previously, he first noted swelling below the right ear. A tonsillectomy was performed and there was noted further enlargement of the mass after this time. "Electric" treatments thereupon reduced the swelling. Later there appeared lymphadenopathy in the axillary and inguinal regions. Adenectomy of the right axillary nodes was performed but upon admission bilateral cervical and axillary lymphadenopathy was apparent. The previously removed nodes had been diagnosed Hodgkin's disease. During the hospital stay, sensory disturbances occurred in the flexor aspect of the right forearm with paresthesias, burning and tingling giving way to deep boring pain. Areas of vesiculation appeared in the course of the cutaneous

nerves derived from C_8, T_1, T_2, and T_3 posterior roots and a diagnosis of herpes zoster was made. (Figure 2.)

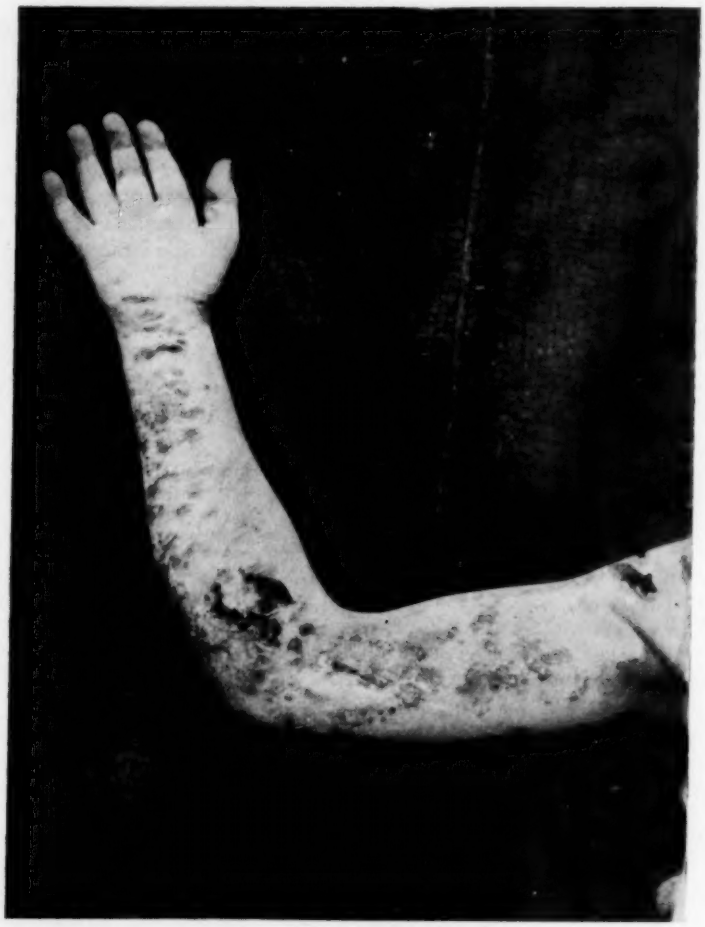

FIG. 2. Herpes zoster complicating Hodgkin's disease (Case 7).

Case 7 presented a classical picture of herpes zoster. In our experience this is an unusual complication of Hodgkin's disease in that it has been encountered in only two other instances. Histologic sections of the involved nerves or their ganglia are lacking and it may well be argued that its occurrence is a mere coincidence. Against this objection may be cited the relatively common involvement of the peripheral nerves in the process, particularly after roentgen-therapy.

IV. BONE INVOLVEMENT

Case 8. A white male, aged 34, complained of a painless growth at the angle of the left mandible for a period of three years with rather marked extension in the eight months preceding admission. A biopsy confirmed the clinical diagnosis of

Hodgkin's disease. Five years and eight months following this diagnosis, after an interval treatment with roentgen-ray, the patient returned with a complaint of sharp pains at the left side of the leg, beginning three months previously and later replaced by a pain in the back that remained localized until he grew tired and then radiating in a belt-like fashion around the anterior portions of the body. There had been a weight loss of 12 or 15 pounds in the preceding month, and insomnia had been quite marked. The roentgenogram showed a destructive lesion in the anterior portion of the body of the seventh dorsal vertebra with marked compression and wedging. (Figure 3.)

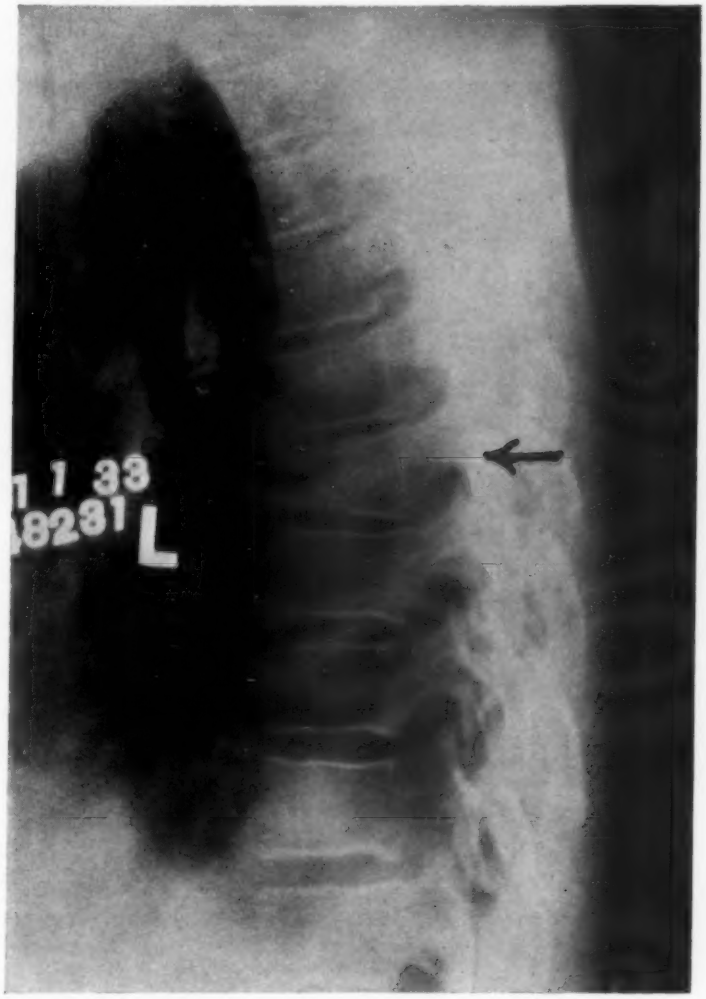

FIG. 3. Hodgkin's disease of the thoracic vertebra (Case 8).

Case 9. A white female, aged 23, complained of "painful glands" in the left axilla. This trouble had started four years previously in the lymph nodes of the neck. A year before admission the nodes in the left axilla began to enlarge. These had become progressively larger in size and definitely painful. Weight loss had been

pronounced and weakness progressive. Two years before admission pain was noted in the right knee and right hip and the left knee and left hip had likewise become involved. Seven months before admission, there was a sharp pain in the left shoulder which lasted for four days. At the same time the painful nodes in the left axilla increased the degree of disability in this shoulder. A weight loss of 14 pounds had occurred in the preceding three years.

The physical examination showed under-nutrition, discrete enlargement of the cervical lymph nodes, similar enlargement of the nodes in the left axilla and smaller nodes in the left epitrochlear region and marked limitation of abduction of the left shoulder. Roentgen-ray of the left shoulder revealed an irregular destruction of the upper end of the shaft and the neck of the left humerus with irregular thickening of the cortex and bony spicules extending out into the soft tissues. (Figure 4.)

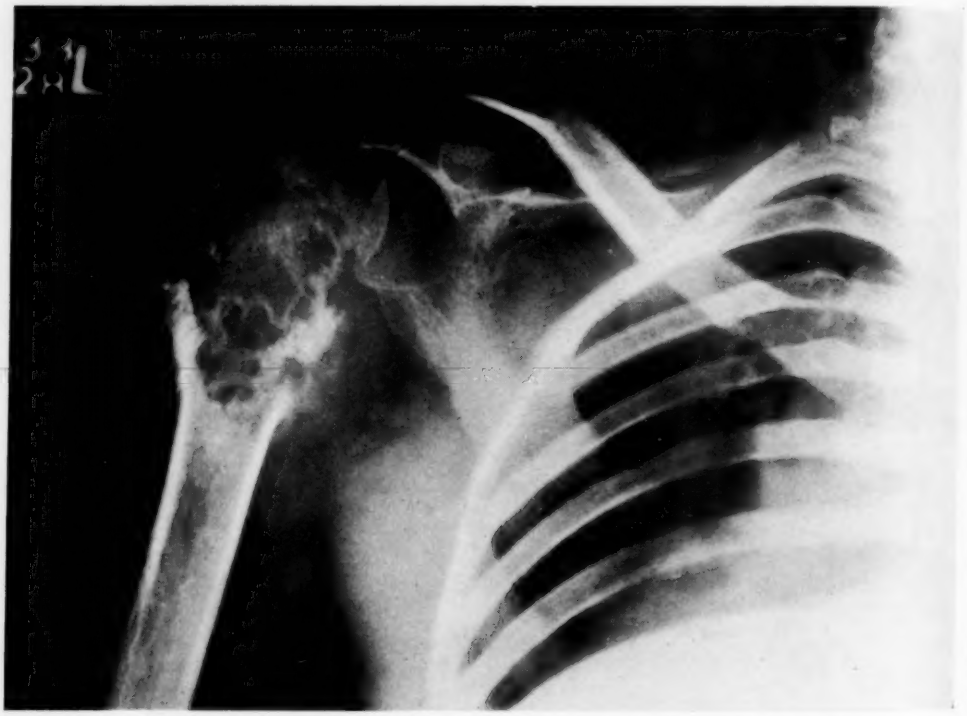

FIG. 4. Hodgkin's disease of the head of the left humerus (Case 9).

Biopsy of an axillary node fixed the diagnosis of Hodgkin's disease. The basal metabolism was plus 35 and plus 34. The blood count showed 50 per cent hemoglobin, 5,120,000 erythrocytes, 18,000 leukocytes with 94 per cent neutrophiles, 3 per cent lymphocytes, 3 per cent metamyelocytes. Relief from pain attended roentgen-therapy and she continued under observation for about two years.

Cases 8 and 9 are interesting examples of the destructive bone lesions of Hodgkin's disease. The implications in the latter are obvious, but in Case 8 there is the added significant detail of girdle pains on the basis of radicular involvement from destruction of the body of the seventh dorsal vertebra.

V. Visceral Involvement

A. Spleen

Case 10. A white female, aged 36, complained of weakness. There was a further history of cough succeeding a cold 17 months previously. This cough was nonproductive and led to a pressing pain in the midabdomen. The appetite became progressively less. Two months after the onset of symptoms, the patient became pregnant. A weight loss of 17 pounds occurred in the ensuing month. Premature delivery at seven months was followed by improvement in appetite and some weight gain. Pain of a continuous and dull order augmented by eating was noted in the epigastrium 14 months before admission and at times this pain was so severe that even the weight of a blanket was uncomfortable. Four months before admission to the hospital, the pain had become more severe and weakness was progressive.

A medical consultation led to the diagnosis of an enlarged spleen, and because of the anemia, transfusions, iron and liver were prescribed. In spite of this support the symptoms progressed without abatement.

Physical examination revealed poor nutrition, icteric pallor, wasting, an epigastric mass, splenomegaly and hepatomegaly, bilateral axillary and inguinal lymphadenopathy. The existence of pruritus was suggested by extensive excoriations. The described lymph nodes were firm, discrete, non-tender and freely movable with relation to underlying and overlying structures. Later some enlargement of the cervical nodes became apparent. The roentgenogram of the chest showed some mediastinal involvement. The basal metabolic rate was plus 38 and plus 39. A biopsy of the axillary nodes showed the characteristic changes of Hodgkin's disease.

In Case 10 the spleen was palpably enlarged but its independent responsibility for the anemia and the epigastric mass was ruled out by a detailed study with the biopsy.

B. Liver

Case 11. A white male, aged 39, complained of a growth in the left groin. Five years previously he had noted a mass the size of a walnut in the left inguinal region and there had been slight but steady increase in its size. Two weeks before admission there occurred a dull ache which was particularly marked when the thigh was flexed sharply upon the abdomen.

The physical examination showed pallor of the skin, exophthalmos, palpable thyroid gland, slight hepatomegaly, splenomegaly and inguinal lymphadenopathy. The biopsy of the inguinal nodes fixed the diagnosis of Hodgkin's disease. The basal metabolism was plus 22 and plus 24. Roentgen-therapy was instituted. After a period of 40 months, the patient returned with a history of the sudden appearance of jaundice a month previously. Anorexia, nausea, vomiting and weakness attended. The stools became clay colored and the urine highly colored. No abdominal pain was noted. In two weeks, 14 pounds had been lost. Reëxamination noted the jaundice with a widespread nonpruritic, papular eruption, exophthalmos, palpable thyroid gland, palpable liver, submaxillary and axillary lymphadenopathy.

An obstructive jaundice was diagnosed from the clinical course, the absence of bile in the feces and of urobilin in the urine. Roentgen-therapy was instituted and after 400 r units to the right hypochondrium in two doses the patient became definitely more uncomfortable without perceptible change in the jaundice. Four days after the discontinuance of the roentgen-therapy, bleeding from the nose, lips, gums and gastrointestinal tract was noted. The stools were bright red from continued bleeding, and the patient died the succeeding day from blood loss.

Extrahepatic biliary obstruction from lymph node pressure upon the common bile duct seemed the simplest explanation for the rapidly developing jaundice in Case 11. Upon this assumption roentgen-therapy was initiated. At necropsy, however, the major biliary ducts were found to be patent, but an extensive cellular infiltration of the liver by the Hodgkin's process had determined the jaundice. Focal hemorrhagic areas were found throughout the intestinal tract.

C. Retroperitoneal lymph nodes

Case 12. A white female, aged 27, complained of pain in the right side of the abdomen. The patient had known of the existence of a lump in the right kidney region prior to hospitalization. The symptoms were those of pressure in this area. She had gained weight and suffered no other discomfort.

The physical examination showed no palpable superficial adenopathy. An irregular tumor mass approximately 6 by 8 centimeters was palpated in the right flank. Fixed and painless, this mass was believed to be either an enlarged kidney or a tumor of the kidney. The laboratory studies, including special roentgenograms, gave no clue.

This patient was interesting because of the inability to fix a preoperative diagnosis, although the consensus favored a renal tumor. An exploratory operation established a lobulated retroperitoneal mass which was excised and proved to be Hodgkin's disease.

D. Mediastinum

Case 13. A white female, aged 50, complained of discomfort in the abdomen which was dated to a dental extraction six months previously. A month later dyspnea appeared when lying on the left side and asthmatic attacks of a severe order would supervene. Relief resulted on turning to the right. This change of position would regularly stop the wheezing. Shortly after this, spontaneous dyspnea appeared and she became conscious of her cardiac action. On several occasions she had a sensation of fainting and would sit down to ward off impending syncope.

Physical examinations disclosed slight exophthalmos, cervical and submaxillary lymphadenopathy and evidences of a superior mediastinal mass with a small fluid accumulation in the left pleural cavity. The fluid withdrawn from the thorax was negative for tubercle bacilli. A biopsy confirmed the diagnosis of Hodgkin's disease.

Dyspnea is a common concomitant of mediastinal Hodgkin's disease, but Case 13 showed the added postural factor in the initiation and the relief of respiratory difficulty.

E. Pleura (and mediastinum)

Case 14. A white male, aged 48, complained that "it was hard to breathe." Five and one-half years previous to admission, he had felt a mass in the upper left quadrant that became painful upon movement. Weight loss and weakness had progressed and there was slight enlargement of the lymph nodes of his neck. In the next six months, these became very large and firm but they remained painless. A diagnosis of Hodgkin's disease was made and roentgen-therapy induced marked improvement. According to the patient's story his health was perfect for a period of five years; but six months before admission the mass reappeared in the upper left

quadrant and the enlargement of the glands in the neck recurred. Embarrassment of respiration developed as a result of the cervical enlargement and roentgen-therapy was initiated. Dysphagia appeared about the time of onset of the dyspnea. The physical examination was particularly significant in the confirmation of the lymph node enlargement and the establishment of enlargement of the liver and spleen. Signs of fluid were found in the right pleural cavity and 1800 c.c. of slightly blood-tinged, straw colored fluid were removed by thoracentesis. Two weeks later another thoracentesis was done and the same amount of fluid removed. The blood count showed a mild hypochromic anemia. The basal metabolism was plus 25 and plus 24 at this time. A roentgenogram of the chest showed a lobulated mass above the cardiac shadow in the superior mediastinum. Fine reticular marking was noted through both lung fields. The right lung base was clouded by homogeneous density.

After several series of roentgen-ray treatments and a progressive decline in the general condition with only mechanical advantages from therapy, the patient died 10 months after the first admission. The leukocytes reached a low level eight months before death, or three months after the first observation in the hospital, at 1,660 with 46 per cent neutrophiles, 40 per cent small lymphocytes and 14 per cent large lymphocytes.

Necropsy in Case 14 showed pleural and perisplenic involvement by the Hodgkin's infiltration in addition to the accustomed changes in lymphoid tissues.

F. Lung (with cavitation and superior vena caval obstruction)

Case 15. A white female, aged 32, complained of a sick feeling. Earlier observations had established the presence of a pulmonary accumulation of pus and Dr. R. H. Jackson resected two inches of the anterior arc of the right fifth rib, sutured the visceral pleura to the parietal layer and two days later aspirated three ounces of purulent material from the subjacent lung. There was some gain in strength but no improvement in the general condition. The temperature was normal for three days after returning home but the cough continued and was productive of large amounts of yellowish pus. On one occasion, six weeks before admission, considerable bright red blood was expectorated. Herpes appeared on the tip of the tongue and on the mucous membranes of the mouth three weeks before admission. Substernal soreness developed and dyspnea occurred upon coughing.

The physical examination at the time of admission was significant in the emaciation and pallor of the subject. The chest findings included marked depression above and below the clavicles, particularly on the right. The expansion was reduced at the right apex and base. The tactile fremitus was decreased to absence below the right second rib. A hyperresonant note was determined throughout the left chest, but there was dullness almost to flatness in the anterior right chest below the clavicle. Over the area medial to the right midclavicular line and above the fifth rib, amphoric breath sounds and whispered pectoriloquy were heard. Interscapular impairment was determined on the right. After eleven days of study, Dr. R. H. Jackson completed a series of exploratory punctures of the right lung under gas anesthesia. Everywhere he met with dense resistance and only occasionally could withdraw a drop of thick muco-pus.

The further course of this patient was marked by progressive decline. Twenty-three days after admission the sternum became more prominent opposite the third costochondral junction, and this prominence was reddened and very sensitive. The right supraclavicular lymph nodes became palpable at this time and the lips and nail beds quite cyanotic. Three days later a second swelling developed in the thoracic

parietes over the right fifth rib about the midclavicular line. Night sweats made their appearance and were quite debilitating. Hemoptysis recurred. Edema of the feet advanced and eventually marked edema of the face appeared. A progressive increase in the venous pressure was noted in the veins of the arms. The prominence over the sternum increased and fluctuation was elicited over the same. Eventually there was some recession of this sternal protrusion. Dilatation of the veins in the right side of the abdomen and increased resistance in the right rectus were noted. Amphoric breath sounds eventually appeared beneath the right clavicle and as low as the second right interspace. The engorgement of the veins in the neck became a prominent feature as did also the edema and cyanosis of the head, neck and arms. She finally died nine months after the first observation in the hospital. From the time of her admission until death, she ran a remittent fever ranging from normal to 104° with a downward tendency of the curve in later weeks, when the range was from 96.4° to 100°. At necropsy, extensive mediastinal Hodgkin's disease was found with invasion of the lung and definite excavation of the process in the right upper lobe. There was likewise direct invasion of the lumen of the superior vena cava by the disease and thrombosis had led to the complete occlusion of this vessel.

The patient presented a difficult problem in diagnosis until accessible lymphadenopathy appeared. Early the presence of a suppurative process in the lung seemed unequivocal. Subsequent aspirations led Dr. Jackson to believe that the pulmonary process was neoplastic. Cavitation of the lung in Hodgkin's disease is not common, but its occurrence has been reported and the signs of excavation should not militate against the diagnosis. Superior cyanosis and edema are sufficiently distinctive to make the intravitam recognition of superior vena caval obstruction relatively easy.

G. Lung (with expiratory *souffle voilé*)

Case 16. A white male, aged 47, first seen in the Out-Patient Department with the complaint of a progressive, painless swelling in the neck, which a biopsy demonstrated to be Hodgkin's disease. The particular interest in this patient arose from the development of unusual signs in the right base ten months later. Evidences of mediastinal involvement (history and physical examination) had existed for six weeks, when there was observed a new phenomenon at the base of the right lung. A period of silence was noted over an area medial to and below the angle of the right scapula on expiration and then a peculiar rush of air and a shower of râles succeeded by an audible cough. This phenomenon persisted for several days and then gave way to an absence of breath sounds over this area. Subsequently, a pleural friction and then signs of fluid made their appearance at this base.

Upon necropsy, three months later, among other findings, the right main bronchus showed some erosion and there was an overgrowth of the mucosa here causing partial obstruction to the right lower bronchus.

A modification of the usual *souffle voilé* is described in Case 16 in that the apparent interference with a free passage of air occurred in the expiratory rather than the inspiratory phase of respiration. A mechanical explanation for this phenomenon was established at necropsy by the changes in the right main bronchus.

VI. Constitutional Manifestations

A. General weakness

Case 17. A white male, 59 years of age, experienced spells of weakness, a run-down feeling and nervousness about three or four months before admission. This nervousness was described as manifesting itself by a quivering of the arms and by such a shakiness of the hands that writing was impossible. Five weeks before admission he accidentally discovered a firm mass the size of a golf ball in the right axilla, which in the intervening period had increased to the size of a baseball.

The constitutional symptoms in Case 17 suggested thyrotoxicosis rather than Hodgkin's disease; but the patient was admitted for study prior to the period of routine basal metabolic determinations in the lymphadenopathies and the diagnosis was reached through a biopsy of the right axillary lymph nodes. The elevation of the basal metabolic rate in the active periods of Hodgkin's disease may at times confuse the diagnostic issue.

B. Suspected focal infection

Case 18. A white female, aged 29, complained of a cough which began a year and a half before, when she began to feel listless and gradually lost weight from an average of 100 pounds to 90 pounds. Her teeth were held responsible for this decline and all teeth in the upper jaw were extracted 14 months before admission. Five days later, swelling in the nodes of the neck was observed and a cough developed which continued dry and unproductive. After a month's time, all of the teeth in the lower jaw were extracted and although there was some subjective improvement, enlargement of the cervical lymph nodes persisted. Five months after this, the symptoms of weakness had progressed markedly and a tonsillectomy was performed. In spite of the surgical procedure, the cervical nodes progressively enlarged and the dry cough continued. Five months later a biopsy was performed and the diagnosis of Hodgkin's disease made. The roentgenogram of the chest confirmed the physical evidence of a superior mediastinal invasion.

This patient had the common experience of many individuals with Hodgkin's disease, in whom an exhaustive search for a focal infectious explanation of the constitutional symptoms proves futile and the diagnosis ultimately is derived by exclusion or by an opportune biopsy.

C. Suspected tuberculosis

Case 19. A white female, aged 26, complained of choking in the neck. She had felt quite well until 11 months previously except for an increasing susceptibility to colds. Succeeding one of these attacks there were marked pleuritic pains in the right chest and these continued from time to time in the interval until her admission. Lack of energy was likewise noted and at the time of admission, she was beginning to have difficulty in breathing, and choking when lying on her back. The complaints had become progressively worse. Enlargement of the nodes in the neck likewise progressed but there had been some subsidence of the swelling immediately to the left of the sternum. On suspicion of tuberculosis, she had been admitted to the sanatorium two months before and had been a bed patient. Constant irritating cough had occurred and there had once been a hemoptysis of one-half cup of bright red

blood. Marked night sweats, fever, dyspnea on exertion and a slight irregularity of cardiac action had been reported.

The past medical history added only the significant details of recurrent tonsillitis and "scrofula" in childhood. The family history disclosed a tuberculous background, the father having died of tuberculosis; a sister and a cousin likewise suffered from tuberculosis.

The patient was unable to lie upon her back. The hands were cool and moist and there were scars in the neck. The anterior and posterior cervical lymph nodes were enlarged. The supraclavicular nodes were particularly prominent. There was slight suprasternal bulging. The described nodes were firm and apparently discrete. There was dullness at the left apex with some impairment at the right base. The breath sounds over the left apex were quite distant. The roentgenogram of the chest showed a dense shadow in the superior mediastinum, largely obscuring the cardiac outline. A dense shadow with an irregular upper border was noted at the right base and a less extensive density at the left base. A biopsy of the cervical nodes established the diagnosis of Hodgkin's disease. A thoracentesis on the right removed 650 c.c. of fluid.

Case 20. A white male, aged 24, complained of pain in the chest. Indefinite gastric symptoms had existed for a year but the pain in the chest dated only five weeks past. A cough with chills and sweats was noted at the onset and there was a severe pain in the upper anterior chest, apparently beneath the sternum. Cough was of a dry unproductive type, and a remittent fever with chills and sweating appeared daily. The patient was confined to bed for two weeks and then began to move about the house occasionally. The dry cough persisted. There was pain in the chest which extended to the lower sternal region. Dyspnea appeared and he was returned to bed under the attendance of his family physician. By the fourth week, the cough became productive of mucus without blood-streaking. He was referred to a tuberculosis sanatorium but the medical director sent him to the Wisconsin General Hospital where evidences of cervical adenopathy and of a pleural effusion on the right were established. One thousand c.c. of fluid were removed from the right pleural cavity whereupon a coarse pleural friction became audible at the base. Bacteriologic studies and animal inoculation of this fluid showed no tubercle bacilli. The biopsy of a cervical lymph node established the diagnosis of Hodgkin's disease.

Cases 19 and 20 illustrate those frequent instances in which tuberculosis is suspected in patients suffering from Hodgkin's disease. In Case 19 the past medical and family histories clearly justified this thought. Furthermore frank hemoptysis had once occurred. Chest pains, cough, fever and sweats completed the masquerade in both cases.

D. Suspected undulant fever (or tuberculosis)

Case 21. A white male, aged 35, complained of "pain around the stomach." His complaint began three months before when he experienced the feeling of oncoming grippe. Following this there was a loss of energy, and a week later coughing in the morning and evening was noted. Two weeks later the appetite was sharply reduced and there were gas pains. Weight loss became apparent and weakness supervened. After slight exertion, he felt extremely exhausted and perspired profusely. A month previous to admission he again consulted a physician who told him that he was running a fever and sent him to bed. After that time, his temperature had ranged from 100° F. in the morning to 102 or 103° F. in the evening. He was suspected of

being tuberculous and sent to a sanatorium where he stayed for several days, but negative chest findings led to his discharge.

A further confusing factor entered the story in the occurrence of undulant fever in the wife the previous summer. Her complaints had grossly paralleled the patient's. Because of the general occurrence of Bang's disease in his herd he had disposed of all cattle, cleaned his barns and procured a new herd with the exception of the few animals in the first group that had not had positive reactions. However, he had stopped boiling milk about a month prior to the onset of his symptoms.

Physical examination disclosed marked emaciation, a mass in the right axilla (which the patient thought had been present for eight years) and a small mass in the left supraclavicular fossa. There were likewise many small nodes in the right supraclavicular fossa. These described masses were non-tender, firm in consistency, and freely movable. The liver and spleen were palpably enlarged, the former extending 8 cm. below the costal margin and the latter 11 cm. The blood count on admission was 48 per cent hemoglobin, 2,050,000 erythrocytes, 4,500 leukocytes, 75 per cent neutrophiles, 24 per cent lymphocytes, 1 per cent monocytes. A low level of leukocytes occurred three weeks after admission at 2,650, with 80 per cent neutrophiles, 14 per cent lymphocytes and 6 per cent monocytes. A remittent fever with a range of 98 to 104° marked the hospital stay of 42 days and the patient died. Biopsy as well as necropsy findings confirmed the clinical diagnosis of Hodgkin's disease.

The constitutional symptoms had suggested the possibility of tuberculosis in this patient. The coincidence of undulant fever in his wife further confused the issue, particularly since their clinical pictures superficially tallied. The general lymphadenopathy, splenomegaly and hepatomegaly at the time of admission to the hospital simplified the problem and the biopsy clinched the diagnosis of Hodgkin's disease. The anemia and leukopenia in this patient should be especially remarked.

E. Alternating pyrexia

Case 22. A white male, aged 50, complained of a fever of eight months' duration. Actually this patient had not been well since a respiratory infection 11 months before admission, but the febrile reaction began three months later. The first episode of fever lasted for five days and was attended by malaise and aching pains. Since the original attack, there had been recurrences of fever at intervals of four to eight days and the febrile episodes themselves had lasted from one to four weeks. There had been no severe shaking chills but usually the attacks were preceded by a chilly sensation of the back and the temperature ranged from 97 to 104° F. with considerable daily variation. The malaise and general aching had continued with the bout of fever. For a few nights before admission, he had regularly been delirious during the height of the fever.

The physical examination established a cervical, axillary and inguinal lymphadenopathy. The spleen was definitely enlarged. Biopsy of one of the cervical nodes confirmed the diagnosis of Hodgkin's disease. During the period of hospitalization, fever occurred at irregular intervals. The temperature ranged from 98.2 to 103.2° F. in febrile periods which lasted 13 and 14 days, respectively, and the one afebrile interval was of 12 days' duration. The patient left the hospital in a second afebrile period, which had then lasted five days.

Case 23. A white male, aged 11, gave a history of lymphadenopathy of two years' duration, involving particularly the cervical region. A biopsy fixed the diagnosis of Hodgkin's disease and particular interest in this patient attaches to the febrile

course upon the fourth admission. At this time a definitely alternating pyrexia was observed with periods of remittent or continued fever ranging as high as 105° F. and lasting for 11 to 18 days and afebrile periods of 7 to 15 days. (Figure 5.)

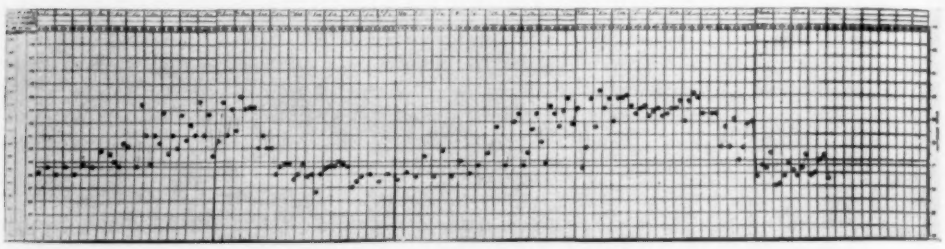

FIG. 5. Alternating pyrexia (Case 23).

Case 24. A white male, aged 37, presented himself because of difficulty in breathing and dated his disability to an attack of pneumonia two years previously. Strength had never been regained from that time and six months before admission he experienced a respiratory infection with chills and fever as high as 103° F. During the past month there was recurrence of the fever and severe pain extending down the right leg. Paresthesias of the feet had occurred the year before. There was a history of roentgen-therapy for masses in the neck a year prior to admission. For a few days there had been a sudden impairment of hearing with headaches. Night blindness had been noted for four or five years.

Physical examination revealed a peculiar dusky pallor with unusual apprehension, restlessness and frequent twitchings of the hands and feet, widening of the palpebral fissure and slight exophthalmos, left cervical lymphadenopathy, splenomegaly and hepatomegaly. The blood count showed 58.4 per cent hemoglobin, 3,015,000 erythrocytes, 5,413 leukocytes with 83 per cent neutrophiles, 0.6 per cent primitive cells, 6.8 per cent lymphocytes, 7 per cent monocytes and 2 per cent large young cells. The eyegrounds showed the characteristic changes of retinitis pigmentosa.

The most significant detail in this patient's clinical course was the continued fever ranging from 103 to 104.8° F. for nine days and then followed by lysis over a six day period to normal. Temperature was maintained at this level for the remaining ten days of the first hospital stay. When he was readmitted 22 days later, another bout of fever was encountered, ranging from 102 to 105° F. until his death three weeks later. His blood count six days before death was 57 per cent hemoglobin, 2,770,000 erythrocytes, 8,800 leukocytes with 94 per cent neutrophiles, 5 per cent lymphocytes and 1 per cent monocytes.

The term, alternating pyrexia, was suggested by Gowers [14] and it is accurately descriptive. At the same time it avoids the controversial issue of priority in the definition of the remarkable bouts of fever interrupted by afebrile seasons in this disease. An erroneous impression should be corrected. While the alternating pyrexia has definite diagnostic value in Hodgkin's disease, it is the least common type of febrile reaction to this condition. Remittent fever is much more common and continued fever is not unusual. As stated before, a fixed regularity in the form and the duration of the phases of alternating pyrexia of Hodgkin's disease may be predicted at times. As a rule the fever is remittent in such bouts. In these details Case 22 falls close to the rule, but Cases 23 and 24 are exceptions. Case 23

ran the alternating pyrexia as a terminal picture and Case 24 had recurrent bouts of continued fever of striking constancy. In any event the diagnostic significance of alternating pyrexia in the presence of even suggestive evidence of Hodgkin's disease should not be overlooked.

VII. Blood

A. Anemia

Case 25. A white male, aged 39, complained of shortness of breath. The present condition was initiated five months previously by pain in his arms extending to his finger tips and a sensation of numbness in the latter. The pain was usually aching and occasionally accompanied by similar discomfort in the legs. "Fatigue aches" the patient termed them. Shortness of breath had progressed and dizziness was observed in the morning on rising. There had been a sore mouth two years previously, relieved by repair of the teeth. Soreness of the tongue over the past year had responded to brushing of the teeth with soda. Extreme night sweats had appeared over the past three months and there had been chills with sweats. Palpitation and dyspnea had advanced steadily as had also the paresthesias.

The physical examination included a yellow pallor, palpable liver and spleen. A few inconspicuous inguinal and epitrochlear nodes were noted.

The laboratory examinations included the blood count: 40 per cent hemoglobin, 1,170,000 erythrocytes, 2,900 leukocytes, without a significant differential change. The gastric analysis showed no free hydrochloric acid, even after the injection of histamine. The icterus index was 8. Urobilin in excess was found in the urine. The basal metabolic rate was plus 30 and plus 29. A diagnosis of pernicious anemia was made. Concentrated liver extract administered parenterally at five-day intervals effected no improvement in the general condition. Because of the poor condition of the patient and the failure of response to liver, a transfusion was done 15 days after admission. A continued observation of the marrow insufficiency, anemia, leukopenia and thrombocytopenia, attracted attention and it was furthermore significant that the improvement from transfusions was not maintained. Finally, 88 days after admission, a small lymph node in the left posterior cervical chain was noted, a biopsy obtained and the diagnosis of Hodgkin's disease made. Whereupon roentgen-therapy was initiated and the earlier advantage of transfusions became very much more pronounced in the improvement of the blood picture. A month later the following level pertained: hemoglobin 70 per cent, erythrocytes 5,140,000, leukocytes 6,850.

The erroneous diagnosis of pernicious anemia in this patient was not discovered until the failure of response to adequate liver therapy led to a search for an explanation. The hypochromic anemia, pigment changes and achlorhydria all added to the confusion. The palpable spleen should have aroused suspicion, but only upon failure of specific therapy was a lymph node excised and the diagnosis of Hodgkin's disease made. The response of the blood picture to transfusions after roentgen-therapy was as spectacular as the subjective improvement.

B. Leukocyte formula in prognosis

Case 26. A white female, aged 41, complained of weakness. Eighteen months previously she had suffered from a sharp rheumatic pain in the right arm, radiating from the shoulder to the elbow and aggravated by motion. This pain continued in

severe intensity for a month and then disappeared to return with cold weather and hard work. For several months before admission the pain had persisted and the patient noted firm lumps in either side of the neck. With effort, as in doing the family washing, the right arm would swell, become blue and paresthesias would occur without actual pain.

The physical examination determined the presence of a pyramid of discrete, nontender lymph nodes in the cervical region with the base at the angle of the jaw. The largest nodes were in the upper end of the chain. Axillary lymphadenopathy and inguinal involvement were evident to physical examination, and mediastinal involvement to roentgen-ray. Upon repeated examinations during the succeeding nine months, the blood count ranged from the initial level of 65 per cent hemoglobin, 6,590,000 erythrocytes, 23,200 leukocytes, 88.2 per cent neutrophiles, 1 per cent eosinophiles, 6.6 per cent lymphocytes, 4.2 per cent monocytes, to a level of 40 per cent hemoglobin, 3,260,000 erythrocytes, 31,800 leukocytes, 96 per cent neutrophiles, 2 per cent lymphocytes and 2 per cent monocytes twelve days before death.

From Bunting's work [9, 10] the leukocyte formula in Hodgkin's disease assumes an exceedingly important place in the prognosis. Clearly the isolated numerical leukocyte count means little in any condition and in this disease a single differential picture avails nothing, but by repeated determinations in skilled hands it is possible in conjunction with the clinical findings to trace the stages and to predict the outcome of this disease with a measure of assurance. The patient passes from a stage of lymphoid resistance with an inversion of the formula to that of lymphoid paralysis when in a terminal period the neutrophiles may number as high as 98.5 per cent of a grossly elevated leukocyte count.

C. Suspected leukemia

Case 27. A white male, aged 39, complained of distress after meals. Until three years previously he had been entirely sound and then suffered from neuritis and a "tired feeling." Tonsillectomy was performed and the patient was much relieved for six months, whereupon early fatigue returned. For 10 months night sweats appeared practically every night. Eight months thereafter thyroidectomy was performed with some temporary improvement. Two months prior to admission he began to lose ground again. Sweats returned nightly and there was considerable distress after meals. A sense of pressure developed half way through the meals and remained two or three hours thereafter. This feeling of distress appeared after every meal. There was a 10 pound weight loss before admission.

The physical examination revealed a sallow complexion and red beefy tongue with prominent fungiform papillae. Marked enlargement of the liver and spleen and free fluid in the abdomen were noted. A few supraclavicular nodes were palpated. The blood count on admission showed 55 per cent hemoglobin, 3,690,000 erythrocytes, 58,000 leukocytes, 92.75 per cent neutrophiles, 0.25 per cent eosinophiles, 4.5 per cent lymphocytes and 2.5 per cent metamyelocytes. Basal metabolism was plus 32 and plus 35. A high point in the leukocytes was reached 13 days after admission at 71,000, 91 per cent of which were neutrophiles.

A diagnosis of chronic myelocytic leukemia was maintained for some time until the persistence of the above leukocytic formula, remittent fever, lymphadenopathy and the clinical course necessitated a review of the im-

pression and the consideration of Hodgkin's disease. A biopsy confirmed this diagnosis.

D. Leukopenia

Case 28. A white male, aged 35, complained of swelling of the "glands" in his neck, which dated back three months and was first noted as a part of a general lymphadenopathy. After a period of roentgen-therapy in the hospital, he was treated as an outpatient on two occasions over the next six months. An interval of eight months elapsed before a readmission, at which time he reported an interval of freedom of symptoms and of regained weight and strength during the summer of the previous year. With the return of cold weather the lymphadenopathy had recurred and there was pain in the left lower quadrant. Weakness and fatigue marked the subjective picture at this time. There was general lymphadenopathy and hepatomegaly. A further series of deep roentgen-therapy was administered at this time. The patient returned to the hospital four months later with a history of further fatigue and bleeding of the gums. After a rest period of a month, he returned obviously in a sharp relapse with marked pallor, marked exophthalmos, enlarged liver and spleen and general lymphadenopathy. The interesting change in the advancing anemia and leukopenia reached an extreme point in the latter detail with 450 leukocytes, 35 per cent neutrophiles and 65 per cent lymphocytes, three days before death. At this time the hemoglobin was 45 per cent and the erythrocytes 2,490,000.

Naturally the contribution of roentgen-therapy to the profound leukopenia in Case 28 must be seriously considered. In our judgment it was an important factor in this instance, but the natural occurrence of a grave leukopenia has in several other patients led to a suspicion of an aleukemic leukemia and the necessity for a marrow biopsy where accessible lymph nodes were not enlarged. Boyer's recent review of leukopenia in Hodgkin's disease [15] is very illuminating.

VIII. Concurrent Tuberculosis and Hodgkin's Disease

Case 29. A white male, aged 48, gave the history of axillary lymphadenopathy of seven years' duration, succeeding a felon on a finger of the left hand. Removal of a lymph node from the left axilla ten months after the onset led to a diagnosis of Hodgkin's disease. After a further interval of eight months more nodes reappeared in the left axilla and grew to the size of a grapefruit. Roentgen-therapy led to some subsidence, but there was later enlargement of nodes in the right axilla and also in the cervical region. Further roentgen-therapy was applied but the nodes had recurrently appeared in intervals between the treatment.

Upon physical examination the nodes in the cervical region were small, discrete and non-tender. Similar nodes were defined in the inguinal region. The nodes in the axilla, however, were slightly tender, confluent and adherent. The biopsy was illuminating in that the coexistence of tuberculosis and Hodgkin's disease was established.

Case 29 merely substantiates Ewing's statement, "Tuberculosis follows Hodgkin's disease like a shadow." [16]

This brief review of the experience in one clinic emphasizes the necessity for diagnostic awareness of the possibility of Hodgkin's disease in a

number of guises. Clearly the clinical pattern must not be too sharply drawn or many cases will escape early recognition. The constitutional and hematopoietic reactions of the disease appear to be especially susceptible of misinterpretation unless the diagnostic consciousness of these possibilities be ever present at the bedside. Finally the laboratory aids to the diagnosis should be regularly invoked. The blood picture, in expert hands, has certain diagnostic features; but even disregarding this somewhat controversial issue, invaluable prognostic information may be gathered from the routine study of the differential formulae of the leukocytes upon frequently repeated studies through the course of the disease. Basal metabolic studies give unequivocal evidence of the activity of the process, but no diagnostic inferences may be drawn from the same. The biopsy of accessible lymph nodes frequently fixes the diagnosis and even upon suspicion should be regularly employed in this relation.

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THE INTERNIST AND THE SYPHILIS CONTROL PROGRAM *

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AMONG the objectives of the American College of Physicians that have been enumerated in the articles of its Constitution are: "maintaining and advancing the highest possible standards in medical education and medical practice; . . . maintaining both the dignity and efficiency of internal medicine in its relationship to public welfare; . . . to foster measures for the prevention of disease and for improving public health." If the College is to maintain these purposes and ideals, the fullest participation on the part of the membership is required in the current program for the control of syphilis, for this is the major public health effort of this decade.

The first paper in the first number of the first volume of the ANNALS OF MEDICINE (the precursor of our ANNALS OF INTERNAL MEDICINE) contains the following statement: "The exponent of internal medicine must know syphilis in all of its manifestations and its results. For its widespread incidence must always be taken into account as modifying disease or dominating therapy throughout the whole field of internal medicine." Thus did the president of the American College of Physicians in 1920, Dr. Reynold Webb Wilcox, in an address defining the range and scope of internal medicine, lay claim to the disease, syphilis, as rightly belonging in the domain of the internist. I suspect that Dr. Wilcox was moved to make these remarks because of the neglect of the disease by his colleagues and because he had witnessed the tendency on the part of urologists and dermatologists to seclude it in the field of their activities. His remarks may have been intended to constitute protest. However this may be, I am sure we can agree that it was then and is now a most desirable thing that medical men exhibit a keen interest in this infection. Lay and professional concern regarding syphilis is mounting steadily. It is, therefore, proper that the internist look critically at the problem as it affects his practice and the public health, admitting, insisting upon, a share in the responsibility for preventing, diagnosing, treating and, when possible, curing this malady.

Those most interested in the syphilis control program expect much of the members of this College. It is felt that the position of the internist in his community is such that he will be peculiarly effective in encouraging professional and lay education, in engendering an enlightened, aggressive attitude toward the syphilis problem, in stripping it of prejudices and taboos in order that scientific medicine may better realize its possibilities. Are internists really in a position to play so important a rôle in the program? An affirmative answer is inescapable. The internist's training is such that

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he understands the significance of the term "generalized infection" and is cognizant of understood and obscure factors which operate in infectious disease. The patient and, alas, often the urologist and dermatologist may be seriously concerned in acute syphilis only with a genital ulcer or an exanthematous eruption. The internist recognizes that long before these lesions have made their appearance, the virus of syphilis is widespread throughout the body. Of tremendous importance from the standpoint of spread of disease and, therefore, of the public health, the superficial early lesions have no more clinical significance in the patient's health than the localized, granulomatous ulcer marking the site of entrance of *B. tularense* in tularemia or the rose spots scattered on the skin of the abdomen in typhoid fever. The internist knows from sad experience that the immediate threat of acute syphilis is not directed against the patient's health but against his or her contacts (the public health);—that the ultimate threat is against the cardiovascular and central nervous systems. Because he is familiar with chronic disease the internist can appreciate the significance of the term "latent syphilis" with its sinister implication that latency may be followed by activity. Furthermore the disciplines which the internist has experienced render him respectful of learning and eager for guidance when the latter is authoritative and based on scientific study and accomplishment. Data dealing with the relative value of various methods of diagnosing and treating syphilis have been accumulated. Now one can say that there are proper and improper methods. Facts have supplanted opinions regarding many treatment problems. There is irrefutable evidence that these facts are not being utilized by the majority of physicians treating syphilis. The internist appreciates the gravity of the implications of this statement, for he encounters the results of poor treatment in patients with cardiovascular, central nervous system and congenital syphilis. It is high time that he interest himself not so much with discouraging studies relative to this or that method of treating syphilitic aortitis, syphilitic hepatic cirrhosis, tabes and paresis, but with the application of his knowledge and skill to the prevention of these often irreversible, lethal conditions. This he can do if he will accept as his own the problems of preventing and treating acute and latent syphilis.

Is it worthwhile? Is syphilis so important after all? "The high incidence of known cases seeking treatment, the ratio of early syphilitic patients under treatment to the exposed contacts infected (for two individuals with early syphilis who seek treatment there are three exposed contacts infected) and the accumulating number of untreated or inadequately treated individuals with syphilis are the basis for the estimate that one out of ten adults in the United States today has or has had syphilis."[1] "A half million people acquire syphilis each year in the United States or one and one half times as many as acquire tuberculosis."[2]

It is estimated that there are at least 25,000 fetal deaths from syphilis

in the United States each year.[2] It is believed that 40,000 deaths from cardiovascular syphilis occur annually. Vonderlehr has estimated that each death represents a loss of from 19 to 23 years of life with the result that the total loss from cardiovascular syphilis is from 800,000 to 850,000 years of life annually. There is a minimum of 4,500 deaths per year from paresis and 1,100 from tabes. "Since each death from paresis represents a loss of about 22 years of life and each death from tabes a loss of about 14 years of life," Vonderlehr estimates that the total loss from these two conditions is about 100,000 years of life annually in the United States. Thus it is seen that the United States population loses well over 900,000 years of life annually from cardiovascular syphilis, tabes, and paresis. The cost of the disease is apparent in terms of morbidity and mortality. The cost in dollars and cents to taxpayers, philanthropic boards, and private patients for institutionalizing for many years the physical derelicts of the disease is formidable. I shall not attempt a consideration of it. Suffice it to say that the cost is obviously far greater than for any plan for control, however expensive the latter may be.

Is it feasible to attack the problem? What weapons have we, and are they effective? The etiology of the disease is known. We have accurate tests for its presence. The diagnosis, in cases which can be effectively treated with present methods, is not difficult. Treatment, though far from ideal, is effective, if properly applied, in (*a*) curing and rendering non-infectious the vast majority of patients with early syphilis; (*b*) in preventing congenital syphilis; (*c*) in protecting patients with latent syphilis from the sequelae of chronic infection; and (*d*) in prolonging life and comfort in the established, chronic disease. If our present knowledge were utilized to its fullest, the disease could be promptly brought under control. To this end, a program, sponsored by the United States Public Health Service under the leadership of Surgeon-General Thomas Parran, has been formulated. This program involves education of profession and public as to both the menace of the disease and the possibilities of its control; the improvement of facilities for the care of patients of all economic groups; the development of a public health attitude toward the disease with special emphasis on case finding through contact studies; rendering patients with acute syphilis non-infectious by proper treatment; curing, when possible; and preventing congenital syphilis. To this end the practitioners of the country, who care for over half of the syphilis which is recognized and under treatment,[3] and the public health forces are being organized for the attack. Is it not fitting that we consider and establish our position, as internists, in this undertaking?

The first and most effective thing that the individual internist can do to contribute to the success of this control program is to familiarize himself with modern concepts of diagnosis and management of the disease—to learn and practice sound medicine in so far as syphilis is concerned. No more important step could be taken toward the successful consummation of this

program than that the internists of the country give syphilis its proper place in their discussions, thought and practice. How many internists are actually mindful of the following facts relative to syphilis: that it is a generalized infectious disease long before the appearance of skin and mucous membrane lesions; that the acute stage of the disease is a critical period in the life of any syphilitic from the viewpoint of the public health since it is the time that he or she infects others; that the early acute phase of the infection is the time during which the spirochetes are disseminated throughout the body; and that it is the time of the laying of foundations for the later development of cardiovascular and central nervous system disease; and, finally, that the acute disease is clinically curable.

Are these important facts known to all internists and, if they are, are all internists duly impressed with the great opportunity for prevention and cure that each patient with acute syphilis presents? Is it common knowledge that the present standardized methods of treatment for acute syphilis, involving scheduled treatments for well over a year, are greatly superior to other treatment plans and that the patient's chance for cure is dependent upon such management?[4] Do all good physicians use these methods? Does every patient with acute syphilis raise a question in the doctor's mind as to the existence of unrecognized contact infection? Does he try to find the source of his patient's disease and render it non-infectious? Does he think of syphilis and its threat whenever he sees a pregnant woman and does he insist upon a serological test for its presence or absence? The answer to most of these questions is in the negative. The medical profession in general, including internists, must admit to an attitude of casualness and indifference with regard to syphilis, which is, to say the least, inconsistent with medical traditions and ideals.

What, to be specific, should the intelligent internist know and do? What are the " minimum requirements " with regard to attitudes and practice?

First, know and teach that syphilis is highly infectious during its acute phase and that for every case of acute syphilis there is a source and that this source spreads disease.

Second, know and teach that the foundations for serious, late manifestations of syphilis are laid in the early stage of the infection.

Third, know that the acute stage is the important stage to treat—both from the public health point of view and also from the point of view of the patient's future health. Here is the golden opportunity to practice both preventive and curative medicine.

Fourth, remember that even after the golden opportunity has passed, congenital syphilis can be prevented and many of the sequelae of syphilis can be forestalled by adequately treating latent or chronic syphilis.

We shall see in this generation a marked reduction in the incidence of acute syphilis in the United States. Many of us will live long enough to witness a reduction in the incidence of congenital syphilis, neuro-syphilis,

cardiovascular and visceral syphilis. Bereft of its age-old prejudices and taboos the syphilis problem is being presented to the medical profession and to the public. Means to cope with and to solve this problem are at hand. They are admittedly not ideal but they are, nevertheless, effective. Failure of the current program could be attributed only to lack of intelligent co-operation on the part of all parties involved—a most important group being, for reasons which I have indicated, the internists.

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PROGNOSIS IN TUBERCULOSIS *

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Introductory

When one considers the prognosis of tuberculosis in its widest implications he is obliged to extend his discussion to every phase of the tuberculosis problem and consider every factor which influences bacillary growth and activity or modifies individual resistance. The outcome of the disease is influenced by the virulence and numbers of infecting bacilli; the type of the disease and its severity; the constitutional peculiarities of the patient; his general reacting powers; his condition at the time when infection occurs; the character of the tissues which are involved; the nature of the lesion; the time when the diagnosis is made; the character of treatment and when it is instituted; the age, economic and social status and intelligence of the patient; the character of the climate and weather to which the patient is exposed; the psychology of the patient and of the friends who advise him; the physician who carries out the treatment, his psychology as well as medical knowledge and experience in meeting the problems of the tuberculous patient; the place where the treatment is to be carried out whether at home, in a sanatorium or in a dispensary; and many other factors of greater or lesser import.

It is not always the big thing that determines the outcome in tuberculosis. We at times see the prognosis changed from favorable to unfavorable and the reverse as a result of some very small factor which might, under ordinary conditions, seem of minor importance.

In the time allotted to this paper I shall confine myself largely to the influence which a competent physiologic reaction and a competent compensating mechanism on the part of the patient has upon the prognosis of tuberculosis; and further point out the difference in a prognosis from the standpoint of healing and from the standpoint of physical efficiency.

Two Basic Factors on Which Prognosis Depends

The healing of tuberculosis is a physiologic process; and, when the physiologic balance of the patient is good, tuberculosis shows a strong tendency to heal. That the prognosis is favorable, provided the disease is treated intelligently in its early stages, is now generally acknowledged, because the patient's resisting power is good and the ability of the lung tissue and thoracic cage to compensate for the loss which results from infiltration cavity or fibrosis is excellent. When these early cases fail to heal it is usually due to the fact that conditions necessary to the healing process were

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not established. That the prognosis is less favorable in the far advanced stages and when improperly treated in all stages is equally well established.

With the well established forms of treatment everywhere recognized today, there are few places in civilized countries where a patient suffering from tuberculosis can not be given a fair chance of recovery if aid is sought at a time when the disease is curable. This is very different from what it was a quarter of a century ago; for even so recently as that, well trained specialists were few, the general opinion of physicians was that the disease was hopeless, and the aid necessary to cure was rarely to be had.

The two most potent factors in changing the prognosis of tuberculosis in recent years from the status of an all time hopeless disease to that of one that is curable have been the large group of medical men who have made tuberculosis their special study, and the systematic spread of knowledge concerning the nature of the disease by interested workers. It is almost an unbelievable fact that this change in prognosis has come within a single generation.

Next Step in Improving Prognosis

Probably the next greatest advance in prognosis will be brought about by the medical profession considering tuberculosis in the same category as other diseases. General medical men should understand tuberculosis and show the same interest in it that they show toward diseases of the heart, kidney and gastrointestinal tract, or diabetes or blood diseases. When they do this we may hope not only for an earlier recognition than today, but also for the application of treatment when it will be more effective. In no disease can a physician render a greater service to a patient or to his family than in making an early diagnosis of tuberculosis and directing him so that he at once receives adequate treatment and at once minimizes the danger of infecting others. It not only means saving the patient's life and restoring him to usefulness, but saving others who associate with him from infection. The importance of instituting immediate treatment is particularly emphasized by the fact that the disease so often affects the bread-winner and is so often found in the years of early adult life when the domestic, economic, social and cultural interests of the family depend upon the patient's ability to carry on with as little loss of time and efficiency as possible.

Prognosis as It Relates to Immunologic Reaction

In order to make an intelligent prognosis we must understand something of the intimate reactions which make up the defense mechanism of the patient, for these are basic in prognosis. They vary greatly in different individuals. Tuberculosis is a chronic inflammatory disease. The accompanying inflammation is due to the reaction between bacilli and their products on the one hand, and the tissues of the patient on the other. The reaction, being inflammatory, carries with it local irritation of cells, dilata-

tion of blood vessels, and an exudation in the tissue spaces with an increased serum and cellular content at the site of the injury; all of which belongs to the defense reaction.

Both bacilli and tissue cells may be destroyed as a result of the conflict which goes on for mastery. As a result of the irritation and destruction of tissue cells, enzymes are set free which produce bacteriolysis. Destruction of bacilli is further carried on by cells which possess phagocytic qualities. Resulting both from the growth and the destruction of bacilli, substances are set free into the tissues which gain access to the circulation and stimulate the defensive function of cells throughout the body. Thereafter, when bacilli or bacillary substances gain entrance to the tissues they are anchored and destroyed with increased avidity.

Local defense takes upon itself two forms, one that of bacteriolysis, the other that of tubercle formation; the one primarily destructive of bacilli, the other primarily fixative in that it tends to hold them in situ.

General defense, on the other hand, consists in establishing an increased power on the part of the tissues generally for opposing both bacilli and bacillary products. While certain cells normally have greater defensive powers than others, it seems that every cell of the body is endowed with the function of defense and that it is stimulated to unusual proportions as a result of infection. We call this increased defense immunity. This increased physiologic reaction is the factor which makes it possible for the organism to oppose successfully millions of bacilli in advanced extensive tuberculosis, although first infection may have been brought about by a very few.

While the defense strategy of the body, in case of an attack of microorganisms, consists in concentrating its most effective forces at the point of invasion it carries out the principle of universal conscription and arms all cells so as to guard every area of the body from attack while continuously sending up new forces to the front so as always to have fresh troops guarding the most exposed areas.

In order to understand how prognosis may be modified by the general condition of the patient it is necessary to understand that specific defense is a quickened and heightened response of a physiologic function normally possessed by the body cells; and, that this function is just as normal as that which produces secretions having special properties or that which produces muscular action. So, warding off infection, destruction of invading microorganisms, and the repair of the injury which has been caused are all physiologic processes, the competency of which depends much upon the condition of the patient.

The body's defense is sufficient as a rule to either wholly destroy the few bacilli which enter the tissues at the time of first invasion; or, to hold them largely fixed at the point of entry and in the lymph glands which drain the infected area. But the fact that infection is established is evidence that the numbers of bacilli are greater than the local cells, with their normal

protective function, are able to cope with; and, furthermore, it is evidence that unless this protective power can be increased the infection cannot be successfully opposed. The general principle in physiology of increased response to unusual stimulation now quickly comes into play, and within a few days after bacilli have become implanted in the tissues all cells of the body are able to put up an augmented defense. If tuberculosis extends thereafter, it does so against increased opposition which tends to restrict the extent and severity of the metastases. The prognosis in the more simple lesions which succeed the primary complex is determined very largely by the degree of competency of this protective mechanism.

Tuberculous infection, opposed by increased cellular defense, results in the so-called "adult type of infection." In the adult type, on account of this increased cellular defense, the lymphatic route of spread which was open and free to bacilli at the time of first infection is now largely closed, shutting off the easiest route for bacilli to follow in spreading throughout the body. Bacilli which enter the tissues by way of the blood and canalicular routes such as the bronchi now also meet with increased opposition to implantation and are often destroyed without producing infection; or, if infection is established, it often becomes abortive. This protection in the previously infected individual is so efficient that, unless the numbers of infecting bacilli be great, there is little danger of permanent metastases forming in the early stages of the disease provided, of course, the patient is put at bed rest and so treated as to maintain a normal physiologic response. The increased local and general physiologic responses of the body, if only the patient is maintained in a state of high physical fitness, make the prognosis in early clinical tuberculosis almost invariably favorable.

Prognostic Significance of Caseation

While the major pathologic processes may be described as predominantly exudative and predominantly proliferative, the most serious phenomenon which is met in the pathology of tuberculosis, the one which carries with it the possibility of affecting prognosis most unfavorably, is caseation and softening, because this process is responsible for cavity formation and furnishes the source of bacilli which produce metastases by spreading through such natural channels as the bronchi.

A patient may be incapacitated by the gradual encroachment which a preponderantly proliferative lesion makes upon his reserve pulmonary tissue; but sooner or later caseation with destruction of tissue and cavity formation will usually accompany and increase such incapacity. It is caused by a violent protective reaction of immunized tissues against an unusual number of infecting bacilli or large quantities of their protein products. Multiple cavity can be largely prevented by the immediate application of adequate treatment while the disease is early.

Caseation often takes place early in exudative infections because the tis-

sues are in a state of hyperergy. The anchoring ability of the cells is so great that the protein is fixed in such large quantities that it obstructs the capillaries, cuts off the blood supply to the tissues, and causes them to caseate and undergo destruction; but as the tissues become more accustomed to the infection it seems that the degree of protection becomes greater while the cellular reaction becomes less violent. This is of great prognostic significance, for either a degree of desensitization of the cells takes place or the protein is prevented in some other manner from producing severe localized reactions. While cavity often accompanies an early exudative lesion, a second one rarely follows immediately thereafter, even though the infection continues to spread; and furthermore, few relatively large cavities appear during the course of chronic proliferative lesions except as a result of the fusion of smaller ones. This highly protective mechanism can be relied upon as being the greatest factor in the healing of tuberculosis. Even the extent of destruction may be kept to a minimum by taking advantage of it by the modern methods of treatment which limit the danger of metastases forming by keeping the patient in a state of high physiologic balance. This may be accomplished by the application of rest and other proper physiologic therapeutic measures immediately on the infection assuming clinical importance.

Even a large cavity, today, is far from being the hopeless phenomenon that we formerly thought. The early freshly formed cavity, unless it be situated unfavorably, will usually heal spontaneously, if the patient's reacting powers are quickly brought to a state of efficient action, for the pulmonary tissues are able at this time to take on emphysematous change, and the bony thorax is able to reduce in size and lessen its movement, and these together bring about the conditions required for healing. However, unless cavity is treated properly, it reacts very unfavorably upon prognosis, for it reduces the chances of healing and furnishes an open focus from which bacilli can readily spread and form other metastases.

Prognosis Improved by Artificial Compensatory Measures

Up to the present time most patients who have been treated for tuberculosis have been treated after the disease has become advanced. In these cases both the physiologic balance of the patient is severely disturbed and the mechanism by which compensation takes place between the lung volume and thoracic cage has already been utilized to its limit. So physicians have spent their energy attempting to overcome the many discouraging conditions which this chronic infection presents. However, they have been unwilling to accept defeat and by their ingenuity have devised measures with which to cope with many of the mechanical conditions which adversely influence the prognosis in these cases. The physiologic factor, too, is gradually becoming better understood, but there still is no way of restoring the function of exhausted cells. In healing tuberculosis, nature lessens respiratory move-

ment and reduces the size of the thoracic cage to adjust to the volume of pulmonary tissues as it is reduced by the disease. The tissues adjoining infiltrations in the lung also adjust by becoming emphysematous and enlarging, thus relaxing and compressing the infiltrated and excavated tissues.

Experience has shown that these results may be attained artificially by utilizing relaxing and compressing measures, such as weights upon the chest wall, pneumothorax, pneumoperitoneum, paralysis of the diaphragm and thoracoplasty. These measures promote healing mechanically by reducing respiratory movement, relieving diseased pulmonary tissues of tension, and compressing them. In many cases of advanced tuberculosis these measures bring about favorable mechanical conditions without which a physiologic balance, no matter how stable, would be unable to produce healing. However, no matter how frequently healing follows, it must be understood that the protective and reparative processes depend upon the patient's physiologic response.

Prognosis for Healing and Efficiency Differs

Through relaxing and compressing measures the prognosis in many cases of severe and serious tuberculosis has now become fairly favorable from the standpoint of bringing the disease to a state of quiescence or arrest. This is truly a great accomplishment, but it is still unsatisfactory in that it too often restores a mechanism, which has been injured by neglect, to a limited capacity when our knowledge and understanding of the problems involved warrant a restoration to full capacity. Any measure that carries with it an avoidable reduction in the patient's future efficiency, no matter if the tuberculous process is healed, has in it elements of defeat which medicine must overcome.

To make my meaning clear it is only necessary to contrast the health and full efficiency which a patient suffering from an early limited lesion usually secures through treatment, with the handicap of limited efficiency and insecurity which he usually obtains through the most effective treatment possible when the lesion is far advanced. When we see the interference with the mechanics of respiration, the reduction in lung volume, and the resultant inability to compensate and measure up to the calls for extra physical exertion which is a common occurrence following the best result that can be attained in many far advanced cases of tuberculosis, we should be led to bend every energy towards securing treatment at a stage when such handicaps would rarely follow.

Discussion

From the preceding discussion it may be established that in combating tuberculous infection and in promoting healing we are dealing with functions with which the patient is normally endowed. If cure is accomplished, the patient accomplishes it through these normal functions. If we, as physi-

cians, improve the prognosis, we do it by increasing the patient's own powers and facilities, not by adding something new and extraneous. If only we bear in mind that the phenomena which we meet in the tuberculous process; the proliferation, the exudation and the necrosis, are intimately connected with the immunologic and healing processes, which in turn depend upon the physiologic mechanism of the patient, we will be able to make a more accurate prognosis.

In regard to prognosis it can be said that with stable physiologic equilibrium and favorable conditions for compensatory adjustment on the part of an individual, a limited infection produced by a relatively large number of bacilli, or a smaller number of relatively virulent bacilli, may readily heal; and an infection which may occur at a time when the host's physiologic equilibrium is temporarily lowered may be healed by restoring his physiologic processes to normal; but, should an infection be large or the bacilli be extra virulent, or should the host's physiologic processes remain in a condition of instability for too long a time, then healing of the process may not only fail to take place but metastases may form creating other foci of infection, and from these further metastases may take place, repeating the cycle until healing may become impossible.

While mildly reacting limited lesions are comparatively easy to overcome, multiple or extensive lesions produce a proportionately greater disturbance in the host's physiologic and compensatory processes and bring about a relatively greater tax on his defensive and healing powers. So an advanced and advancing process reduces the favorableness of prognosis by presenting greater difficulties to be overcome before healing may be accomplished, and by causing the host's protective and healing mechanism to be rendered less effective for its task. It is self-evident, then, that the favorableness of prognosis steadily decreases as the tuberculous infection extends quantitatively and as the pathologic changes advance in severity. It is likewise self-evident that a rapid restoration of the patient's physiologic functions, among which is that of defense against infection, greatly improves the prognosis in any case.

Theoretically, one should have little fear but that a normal physiologic function on the part of an individual with a limited tuberculous infection would be able to bring about healing provided it is maintained long enough; and this has been proved by many years of experience. Theoretically, one should expect that the more advanced the process quantitatively and qualitatively the greater the difficulty in securing a healing and the less efficient the patient would be thereafter; and, the experience of many years has shown this to be true. Theoretically, advanced tuberculosis with destructive lesions should be difficult and often impossible to heal by any possible restoration of physiologic balance, and many years of experience have also shown this to be true.

The prognosis in tuberculosis is modified by the character of the lesion,

which depends very much upon the individual patient and his particular physiologic reaction. It furthermore is plain that these two factors are largely in the hands of the physician, to be modified through the application of therapeutic measures. Whether the disease will spread or the patient will be able to defend himself successfully against it depends very much upon the treatment which is carried out. Since healing is primarily physiologic this places the burden of prognosis largely upon the physician, for he determines whether or not a proper physiologic balance is established and maintained.

Before the necessity of maintaining an equilibrium between the size of the thoracic space and the lung volume was understood as being a prime factor in prognosis, pneumothorax and other measures of relaxing and compressing the pulmonary tissues were established, and it was thought that their main purpose was compression or enforced rest to the lung. While this is often true in far advanced cases, it is hardly so in those early cases which will heal spontaneously under hygienic measures alone. Compensation in these cases is necessary rather than active compression.

It is generally accepted that pneumothorax has improved prognosis more than any other measure used in treatment. There is no doubt that it reduces the danger of spreading; that it improves the chances of certain advanced cases that were found to be incurable by older methods, and that it gives the physician a control over the patient. It will not only produce favorable results in a very large group of comparatively early cases, but also in another group that rarely heals without some form of artificial aid. This, particularly, is what has made it so popular, for most cases under treatment belong to this class. However, let us not deceive ourselves, for the best prognosis, with or without compression, is found in early cases.

If we were to discuss the manner in which prognosis is influenced by various procedures, we should divide the patients into those in whom artificial compression measures are necessary and those in whom they are not. As it is now, credit is given to compression measures in many instances in which the lesions would have probably healed under hygienic measures alone. Those early cases in which the patient is able to make his own compensation, if collapsed, add to the prestige of pneumothorax, when in reality a similar result could have been obtained without it.

Pneumothorax has become exceedingly popular in instances in which adequate medical supervision cannot be had. The great majority of tuberculous patients are treated in public institutions in which the number of beds is inadequate and the medical service is undermanned. Therefore, it has become necessary to meet the problems with the facilities which are at hand. To do this compression therapy has been used, not so much because it is necessary for healing, but as a matter of expediency in order to make the facilities meet the needs of the community. Early cases in which the question of healing under hygienic measures is hardly questioned are submitted to

compression therapy, the purpose of which is to render patients bacillus-free as quickly as possible and send them back to their homes, leaving the beds in the institution for others.

All of the early cases that are collapsed in this way add to the prestige of collapse therapy. The effect is to brand the prognosis in most cases of tuberculosis as unfavorable unless collapse therapy is used. That such an attitude is wrong may be shown by the statistics of institutions which treated tuberculosis before artificial compression was generally used. How wrong it is cannot be determined until statistics covering many cases treated with and without pneumothorax are analyzed in an unbiased manner. Recent studies from English sanatoria show better results without operative measures while those from Detroit show best results with.

Admitting that artificial compression, particularly pneumothorax, will enable us to secure a healing in many patients in whom we would fail otherwise, let us not forget that rest with spontaneous compensation or spontaneous compensation supplemented by temporary phrenic interruption will bring about healing in a very large percentage of the early cases and restore the patient to health with a minimum degree of physical inefficiency, produced either by the disease or as a result of the therapy. Pneumothorax produces injury to the respiratory mechanism of the patient in quite a number of instances, and in discussing prognosis all such injuries must be considered. Thoracoplasty, which is a boon to the patient who faces the alternative of healing with incapacity of one lung or of remaining ill, cannot be defended as a desirable treatment. It is the treatment that all would like to escape if possible; but the years of life and comfort it adds are a blessing to the one who cannot do better. We hope, however, that its necessity will become less and less as the truths about tuberculosis become more generally disseminated.

Tuberculosis specialists should urge early diagnosis and immediate restoration of physiologic balance as one of the most important factors in improving the prognosis of this disease. No one would take from far advanced cases the opportunity of healing, even though they are seriously handicapped during the rest of their lives, but the fact that these patients with advanced disease can be handled successfully from the standpoint of cure must not blind one to the unnecessary loss of efficiency that is brought about by treating cases which are far advanced instead of early.

The improvement in prognosis which has been brought about by scientific ingenuity should be accepted for what has been accomplished, but it should not satisfy medical men if better results are possible. On the contrary, it should stimulate humanitarian sentiments so that every tuberculosis worker would proclaim long and loud, in season and out of season, that lives and efficiency are needlessly sacrificed by allowing clinical tuberculosis to extend beyond the time when its cure can be brought about in most instances through the stimulation of normal physiologic functions and through na-

ture's own compensatory mechanism, or at most by the use of the simpler operative measures.

Summary

The cure of tuberculosis is accomplished through normal physiologic processes. The lung may be reduced in volume by infiltration, cavity and fibrosis; and the adjustment of lung volume to the size of the thoracic cage is important in healing. In advanced cases healing may be prevented unless such compensation can be made. The prognosis, then, depends upon physiologic competency and compensatory adjustment.

The prognosis for healing and for efficiency differs. The prognosis in tuberculosis in its early stages is favorable for healing, and also for the future efficiency of the patient. The prognosis in far advanced cases, with the newer methods of treatment, is quite favorable for healing, but the prognosis for efficiency is lowered.

The profession should not be satisfied with the present status of therapy. Too many patients come under treatment only when the lesions are of such severity that the measures required to produce healing are so radical as to entail a lamentable reduction in the patients' future respiratory efficiency.

In order that patients may be treated during the favorable stage of the disease, the medical profession should take the same interest in tuberculosis as it does in other diseases; prepare itself for making early diagnoses and understand the principles of therapy, so that proper treatment may be immediately applied.

SCARLET FEVER *

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THE modern conception of scarlet fever may be summarized briefly as follows:

The evidence that scarlet fever is caused by hemolytic streptococcus infection is convincing and this etiology of the disease is generally accepted as proved. The constant association of the clinical disease with some focus infected with these organisms; the production of experimental scarlet fever by purposeful inoculation of susceptible volunteers with cultures of streptococci; and the various biologic reactions produced by injection of hemolytic streptococcus filtrates leave little room for doubt that the hemolytic streptococcus is the essential cause of the disease. As a result of observations on scarlet fever as a streptococcus infection, it has become evident that the disease is a composite one and that the manifestations can be separated into two distinct groups. The first group includes those phenomena resulting directly from infection and invasion of the tissues by the streptococcus and constitutes the *septic* component of scarlet fever. These septic manifestations are clinically identical with those of similar nonscarlatinal pyogenic infection and include the acute pharyngitis of varying degree seen in the usual form of scarlatina, as well as the localized infection of the skin or endometrium noted in the surgical or puerperal types; the direct extension of the infection to adjacent tissues in such complications as otitis, mastoiditis, cervical adenitis, or phlegmonous angina, and the accompanying malaise, fever, and leukocytosis common to acute streptococcus infections of this character. The second or *toxic* component of scarlet fever includes those added manifestations which are caused by the absorption of specific toxic substances derived from the streptococci themselves. All of these can be reproduced in susceptible persons by the injection of sterile streptococcus filtrate and are obviously quite distinct from the changes produced by direct tissue invasion by the organisms. The purely toxic phenomena include the rash with the accompanying enanthem, the initial vomiting, slight general adenopathy, fever, and, in addition, the less constant manifestations of arthritis and hematuria. Although the toxic phase is combined with the septic in clinical scarlet fever, the two processes are immunologically separate. Certain persons, for example, who are immune to the toxic action of absorbed bacterial substances, may suffer severely from scarlatinal streptococcus infection—the *scarlatina sine exanthemate*—and in many fatal cases of the disease death occurs from the septic infection after the specific toxic symptoms have disap-

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peared. Conversely, it has been noted not infrequently that certain children with marked skin sensitivity to the streptococcus filtrate fail to develop scarlet fever after exposure. This again shows the lack of a constant relationship between susceptibility to the toxic phenomena and immunity to streptococcus infection. Those persons, for example, whose cells are very susceptible to the action of streptococcus products, may possess a well-defined tissue immunity to streptococcus infection. Such protection from scarlet fever is probably dependent on local tissue resistance to infection rather than on circulating antibodies.

The relative seriousness of the effects of these two distinct components of scarlet fever is of some interest. In general the septic element of the infection is by far the more important part of the disease. All serious and fatal complications which are observed appear directly attributable to the invasion and extension of the streptococcus infection. While the specific toxic symptoms are clinically more striking and obvious, they are of relatively short duration, in the majority of cases of a mild character, and have usually disappeared by the time any serious septic complications occur. Those very rare fulminating cases in which severe toxic symptoms are followed shortly by death have suggested that the fatal outcome could be directly attributed to the specific scarlatinal toxemia, although even in such instances death might as readily be due to the intense streptococcus inflammation.

While the exact part played by the specific toxic phase in the serious effects of scarlet fever is as yet unsettled, it is difficult to believe that it plays any but a minor rôle. Regarding the infection itself, the conditions upon which individual resistance or susceptibility to the entrance of the infecting streptococci depends and the manner by which the body overcomes the infection are very imperfectly understood and the recent investigations on scarlet fever have furnished no explanation of them. Whether the specific scarlatinal toxemia has any part in making the septic streptococcus infection more serious is still uncertain. Certainly such added specific toxemia produces a more intense clinical illness during the first week of the infection, although in general the complications and sequelae of streptococcal infections without a rash appear to be quite comparable in degree and severity with similar infections of scarlatina with typical toxic rash.

In the past 50 years the morbidity of scarlet fever has apparently increased while the mortality has decreased. The most probable explanation of this is that during this period there has been an increasing percentage of very mild infections. Whether such infections are actually acquiring a less virulent character, or whether many patients now diagnosed as scarlet fever were previously called nonscarlatinal toxic rashes it is impossible to determine, but possibly both factors play a part in the increased morbidity and decreased mortality. In recent years the mortality has varied from 0.5 per cent to 3 per cent, and the normal mortality is considered to be around 2 per cent. As with all streptococcus infections, especially when they occur in epi-

demic form, there are some years in which virulence and mortality are somewhat above the normal rate. It is important to remember such periodical variations in the virulence of epidemics, especially in interpreting the results of therapy, since certain claims for specific therapeutic measures are based on mortality variations well within normal yearly variations. To the laity the term " scarlet fever " still carries a menace to life and hearing not at all justified by the character of the disease as it exists today.

The question of the relationship of so-called nonscarlatinal streptococcus infections or those without the specific skin rash to typical clinical scarlet fever is an interesting one. It is generally accepted that when scarlet fever occurs in epidemic form, certain contacts suffering from typical streptococcus throat infections but with no rash or other specific toxic manifestations, actually have scarlet fever infection without a rash. On the other hand, when similar streptococcus throat infections occur sporadically, they are usually called merely acute tonsillitis and few consider a possible relationship between them and scarlet fever. Epidemiologically, however, the physician who treats scarlet fever finds that the majority of the patients he sees are sporadic cases and have not been in contact with another case of the disease. It has often been puzzling to understand how such a large percentage of patients with a communicable disease could acquire it without apparent exposure. It has, therefore, become increasingly evident from a purely clinical standpoint that streptococci capable of producing scarlet fever are very widely distributed. The problem of the specificity of streptococci causing scarlet fever, therefore, becomes of some importance epidemiologically, and the question of whether a certain strain of streptococcus or several strains, or indeed almost any pathogenic hemolytic streptococcus may cause scarlet fever, must be considered. The classification of these organisms and their identification and separation has been studied by two methods: First, by means of such bacteriological methods as agglutination and agglutination absorption experiments with immune serums, and second, by a comparison of their ability to produce a specific skin reactive toxin, or specific erythrogenic substance which is neutralizable by human or animal immune serums. Several workers have shown, for example, by agglutination tests with immune rabbit serums, that a very large proportion of the strains isolated from scarlet fever had similar agglutinative characteristics and could be differentiated from strains isolated from nonscarlatinal sources, such as local or general pyogenic infections. This strongly suggested that certain strains were specific for scarlet fever. On the other hand it was later shown that the streptococci isolated from early scarlet fever cases not only differed from those from other sources but also differed from those streptococci isolated from patients with scarlet fever during the third and fourth week of convalescence. Such differences suggest that the group relationships demonstrable by agglutination tests may be altered by the environmental factors in the host which change the specific agglutinability of the streptococci, and that

these differences may not be due to inherent strain differences. Eagles, for example, believes that hemolytic streptococci are a group of organisms whose specific agglutinative qualities may be altered by factors operating upon them in vivo. There is much evidence for the belief that with streptococcus infections just as with tubercle bacillus infections, the different types of clinical disease produced may depend not on variations in the strain or type of infecting organism, but on differences in the host himself. While age, portal of entry, dosage and virulence of the infecting agent are of some importance, the varying reactivities of host's tissues, such as cellular resistance, constitution, and especially previous contact with the infecting antigen, must have a large effect on the type, character and severity of the clinical manifestations.

The second method by which attempts to demonstrate specificity have been made, has been the study of the ability of any given organism to produce a scarlatinal toxin, or the specific erythrogenic substance, in culture filtrates. Most streptococci isolated from scarlet fever produce such toxin, although there is a considerable variation in the amount of toxin formed by different strains. Streptococci from nonscarlatinal sources, such as middle ear and mastoid infections in infants or other suppurative lesions, and even erysipelas also produce scarlatinal toxin in a large percentage of cases, and different organisms show a similar variation in titer of toxin. Occasionally strains from nonscarlatinal sources are far more potent in producing it than scarlatinal strains. This toxin from nonscarlatinal sources cannot be distinguished from scarlet fever toxin, since it is neutralized by scarlatinal antitoxin and immunization of Dick positive children by it is followed by the development of negative Dick tests to scarlatinal toxin. As further evidence of the similarity between the toxin produced by streptococci of scarlatinal and of nonscarlatinal origin may be mentioned the effect of various types of streptococcus anti-serums on acute scarlet fever. Many if not all varieties of commercial anti-streptococcus immune serums, such as anti-erysipelas serum and polyvalent anti-streptococcus serum, have the same effect in causing a fairly prompt fading of the rash and other toxic symptoms when administered early in scarlet fever, as does the scarlatinal antitoxin made from strains of scarlatinal origin. It is possible, for example, to produce a Schultz-Charlton local extinction test or local blanching of an early scarlatinal rash by the intradermal injection of 0.001 c.c. of certain commercial anti-erysipelas serums. Since such serums are produced from strains other than those from scarlet fever, it seems evident that nonscarlatinal strains contain the so-called specific erythrogenic toxin with considerable frequency.

From such observations as have been briefly summarized it would seem that there is little evidence that scarlet fever streptococci possess a specificity that distinguishes them from other streptococci; that the potentialities of any streptococcus to cause scarlet fever must depend largely upon its ability to produce the erythrogenic toxin to which patients with clinical scarlet fever are susceptible; that a large percentage of streptococci from scarlatinal and

nonscarlatinal sources can form this toxin, although there is some variation in the amount produced; and, finally, that if all strains of streptococci cannot secrete toxin in sufficient amount to cause the toxic symptoms in susceptible persons after infection, certainly the dissemination of streptococci capable of producing the clinical disease is so widespread that one may well consider any open streptococcus infection as a potential source of scarlet fever. In general, if the infection occurs in a person immune to the toxin because of the presence of specific antibody in his blood, the diagnosis is nonscarlatinal streptococcus disease, whereas if it occurs in a person susceptible to the toxin, the disease is called scarlet fever.

The inconsistencies of this attitude are apparent and there is an increasing tendency among many to doubt whether scarlet fever is to be any longer considered as a distinct disease entity. It seems likely that clinical scarlet fever is merely a toxic syndrome that accompanies hemolytic streptococcus infections in certain susceptible persons, and it would be more consistent to consider it a scarlatinal type of streptococcus infection or a streptococcus infection with scarlatinal toxic reaction.

It has been mentioned that in the majority of cases of scarlet fever infection, the specific toxic symptoms are mild and no attempt at specific therapy appears warranted. In certain patients the toxicity is severe and in these, the injection of serum antitoxin produces a fairly prompt and often striking beneficial effect on the rash and other toxic symptoms. Such an effect, however, is obtained only if the serum is given in the first three days after the rash appears, and if serum is administered later when the toxic symptoms have reached their height, no beneficial results are observed. Serum treatment, even though given early, appears to have little or no effect upon the septic manifestations or on the streptococcus local infection. Frequently patients have been observed in whom early serum treatment produced a prompt and apparently complete cure of the specific toxic phenomena, but later the septic streptococcus disease spread alarmingly and in certain instances was fatal. Indeed as previously cited, practically all dangerous manifestations are attributable to the septic component of the disease and occur or persist after the specific toxemic symptoms have disappeared. The chief function of serum treatment appears to be symptomatic and directed primarily at controlling the toxic symptoms. When these symptoms are mild, the use of serum is not indicated. A striking disadvantage of routine use of serum in such mild cases is the frequency with which various types of serum reactions occur, some of them causing considerably more distress than the scarlet fever itself. There is little evidence that serum treatment affects the ultimate outcome of the infection.

Although it would appear that the specific toxic factor and the specific toxemia play a far less important and serious part in scarlet fever than the septic streptococcus infection, the character of the toxemia and the mechanism of its production are of much interest. There are two main hypotheses

which have been advanced to explain the production of scarlatinal toxemia. These hypotheses are quite different and a belief in one or the other of them alters considerably one's conception of the mechanism of scarlet fever, and one's procedure in attempting to control it. They may be termed the *toxin hypothesis* which assumes that the toxic agent is a primary streptococcus bacterial exotoxin analogous to other such familiar toxins, and the *allergic hypothesis* which asserts that the streptococcus product producing the symptoms is not primarily toxic and that its toxic action is due to an acquired hypersensitivity of the host's cells from previous streptococcus infection. Before speaking of the evidence supporting these hypotheses, these two types of poisons may be briefly defined so that the distinction between them may be more apparent. A true toxin is a substance which poisons or injures normal cells unless such cells are protected by the presence of a specific neutralizing antibody or antitoxin, which is a cellular product resulting from previous contact with the same toxin. An allergen, on the other hand, has no poisonous action on normal cells unless such cells do have a specific antibody which is a product resulting from previous contact with the same allergen or antigen. With a true toxin the specific antibody, therefore, protects the cells from toxic injury, while with an allergen the specific antibody renders the cells susceptible to toxic injury.

The chief observations upon which the toxin hypothesis is based are as follows:

1. The production of characteristic toxic symptoms by the injection of the filtrate into susceptible persons.

2. The appearance of a local area of erythema (Dick reaction) in the skin of susceptible persons after the intradermal injection of filtrate.

3. The presence of a neutralizing antibody in the blood of convalescent scarlet fever patients, of many persons with negative Dick reactions, and also of filtrate-immunized animals. This antibody resembles an antitoxin since (*a*) when the toxic filtrate is mixed with serum containing the antibody, the filtrate will no longer produce a positive Dick reaction on the skin of a susceptible person; (*b*) when the serum is injected intradermally in an early scarlet fever rash, a local blanching of the eruption occurs after a few hours; and (*c*) intramuscular injection of serum in early scarlet fever cases frequently causes a relatively prompt disappearance of the specific toxic symptoms.

4. By the injection of filtrate into persons with positive Dick reactions, using small quantities at first, followed by gradually increasing doses, the Dick reaction becomes negative, and after some weeks the specific neutralizing antibody appears in the blood.

It is apparent from the foregoing characteristics that, under certain conditions, the filtrate is toxic for man and that it stimulates the production of neutralizing antibody. In these respects, the analogy to a true bacterial exotoxin is close. However, in certain other respects the biologic reactions

and properties of the filtrate differ considerably from known soluble toxins. For example, the specific toxicity of the filtrate is limited to human beings, and in animals no toxic symptoms are produced by its injection, in spite of the fact that animal blood contains no neutralizing antibody. Young infants, also, show no toxic effect from the filtrate and have negative skin tests, even though they are unprotected by the specific antibody. Apparently, susceptibility to the filtrate is limited to human beings and acquired after infancy. In addition, the filtrate itself is considerably more stable than a true toxin since its potency is relatively unaffected by heating and by age. These and other discrepancies between the action and properties of scarlatinal streptococcus filtrate and true toxins make it less certain that the former is a primarily toxic substance and suggest the possibility that the toxic effect of the filtrate in man might depend on an acquired allergic hypersensitivity.

According to the allergic hypothesis there exists an unsensitized state at birth but the streptococcus infections during early life and the absorption of specific antigenic substances produced by streptococci incite the production of specific antibody with a resulting cellular hypersensitivity. A later infection by the same organism, if accompanied by rapid antigen absorption, produces a generalized hypersensitivity reaction evidenced by the toxic syndrome of scarlet fever. This reaction desensitizes the patient by the removal of the specific antibody. Sensitized persons may, however, develop streptococcus infection characterized by slow antigen or allergen absorption, and under such circumstances the desensitization is accomplished gradually without production of a generalized scarlet fever reaction. The allergic hypothesis, however, assumes the possibility of another state with regard to the anti-scarlatinal antibody, that is, an anti-anaphylactic state characterized by the presence of a great excess of circulating antibody, which can combine with absorbed allergen in the circulation, and therefore prevent its reaching the sensitized cells. Clinical allergic reactions occur, apparently only when the antigen combines with antibody in the cells, and when antigen combines with free antibody in the circulation no clinical toxic reaction occurs. After an individual, as a result of excessive or continued absorption of the scarlatinal allergen, has developed a large amount of the antibody in the blood, he shows no clinical scarlatinal reaction to later streptococcus infection. It will be seen, therefore, that the allergic state of an individual with regard to the scarlatinal streptococcus allergen at any given time depends upon the amount and location of the specific antibody present. At birth he has none, and, therefore, there is no cellular skin sensitivity to the antigen (as shown by a negative Dick test), and there is no antibody demonstrable in the blood. When, as a result of later streptococcus infections the cells develop specific antibody in them, their sensitivity is shown by the development of a positive skin Dick test but still no circulating antibody is present. It is in this state of sensitivity that a streptococcus infection may be accompanied by the

scarlet fever syndrome, after which the skin cells are desensitized, the Dick test is negative, but there is still no circulating antibody. Indeed—and this is probably one of the most significant observations that favor the allergic theory—not only during the period of the rash, but after the rash and other toxic symptoms have disappeared, the erythrogenic antigen or toxin can be demonstrated in the patient's circulating blood, that is to say, the patient's blood serum produces positive Dick tests on susceptible or sensitive persons. Such an observation of antigen in the circulation after desensitization could be expected in the case of an allergen, but the presence of a true toxin in the blood after recovery from the specific toxemia would appear difficult to understand.

After desensitization, the absorbed antigen again stimulates the formation of specific antibody and sensitization returns, but when antibody is produced in excess by the cells, it appears in the circulation and the individual becomes anti-anaphylactic. In this state, he is immune to the allergic manifestations of antigen-antibody reaction, because when a subsequent streptococcus infection leads to further absorption of antigen, it is neutralized in the circulation and does not reach the sensitive cells. The amount of circulating antibody varies from time to time as recurring streptococcus infection increases its titer, or freedom from the infection leads to its gradual disappearance from the blood, and the consequent unmasking of the cellular sensitivity. The general reaction with rash and other toxic symptoms of scarlet fever occurs only in those persons who develop a hemolytic streptococcus infection with rapid antigen absorption when in this state of cellular sensitivity. During the early progress of the general reaction in scarlet fever, further combination of antigen with intracellular antibody can be suddenly halted by neutralizing the circulating antigen by the injection of an excess of free antibody, thereby creating a state of transferred anti-anaphylaxis.

One final comment may be made on the two hypotheses. Whichever one comes ultimately to be accepted as the true explanation of the scarlet fever symptoms, each of them can be regarded as somewhat unique. If the streptococcus product is a true toxin, it is quite different from other such toxins, chiefly in its relatively weak toxic action and the fact that its activity seems limited to human beings. On the other hand, if the agent is an allergen, the presence of a specific neutralizing or inhibiting antibody and the hypothetical anti-anaphylactic state finds no analogy in other human allergic reactions.

The allergic hypothesis, however, is supported by a wealth of immunologic analogy, and has the merit of offering an adequate explanation for the various clinical phenomena observed in connection with hemolytic streptococcus infections, skin sensitivity tests, and scarlet fever.

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THE PRODUCTION OF EXTRASYSTOLES BY MEANS OF THE CENTRAL NERVOUS SYSTEM *

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THE occurrence of centrally inaugurated heterotopic impulses in the human heart was first reported by Lucke. Auricular extrasystoles were observed in a 54 year old man in association with a skull injury and severe *commotio cerebri*. A year after the injury the disturbance in rhythm had become even more marked, with the occurrence of fairly long series of successive extrasystoles. A second patient, aged 50, was observed, who for about seven years had suffered a compulsion polyuria resembling diabetes insipidus together with a slight fever which exhibited normal diurnal temperature variations. These findings required for their explanation the assumption of a lesion in the midbrain. The condition persisted for several years, after which cardiac symptoms developed, and ventricular extrasystoles were found in the electrocardiogram. No heart disease could be demonstrated. Lucke assumed a central production of the extrasystoles in both cases. In the first case, a *commotio cerebri* and in the second, a lesion in the midbrain had presumably led to a reaction in the region of the parasympathetic nucleus.

Lucke cited as the only previously known phenomenon of similar nature the case described by Külbs of a 16 year old boy who developed a marked bradycardia following a severe emotional upset. The electrocardiogram showed a sinus bradycardia with flattening of the P-wave and ventricular automatism. This observation, however, is of no particular interest in connection with our present concern, the central origin of extrasystoles. Even though we do not believe that the sharp distinction made by Wenckeback and Winterberg between active and passive heterotopy is in complete accord with the multiple possibilities of origin of extrasystoles, still, the occurrence of a compensatory rhythm in a very slow sinus frequence presents a condition which can be termed a normal behavior of the heart, purely passive in origin. In this paper, however, we are considering the more or less " active " heterotopies in the sense of Lewis' " heterogenetic " contractions; that is, true extrasystoles. We are concerned less with the strict classification of extrasystoles or their sharp distinction from parasystoles, for example, than with as fundamental an understanding as possible of the conditions of origin of heterotopy in the individual case. It must be emphasized that responsibility for the origin of clinically observed extrasystoles can never be attributed solely to a single cause. The occurrence of an extra-

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systole is bound up with a definite situation originally created by the combined effect of many single conditions. From such a standpoint, and in view of the experimental results shortly to be described, it seems to us that in both cases reported by Lucke, the assumption of a central stimulatory effect as the initial cause of the extrasystoles is very likely valid.

If we assume the central origin of heterotopic stimulus formation in the heart, then the only pathway for the transmission of the stimulus that can be considered is that of the long cardiac nerves, particularly the vagus. Until recently the difficulty of such a conception lay perforce in the fact that no action of the vagus on the ventricles of the mammalian heart could be demonstrated. Direct vagus action is unlikely according to the most recent investigations as well. However, Scherf's very searching studies of the origin of extrasystoles show that there certainly exists an indirect vagus effect upon stimulus formation by tertiary centers. He was able to demonstrate a paradoxical effect on mammalian hearts poisoned with aconitin. Along with the normal blocking effect on the sinus node, there occurred ventricular extrasystoles. This indirect vagus effect is apparently to be explained by the arrival of the vagus affecting substance from the auricles to the ventricles, at the circulatory pathway, where it influences the damaged, peculiarly sensitive tertiary centers in paradoxical fashion. Engelhart found a much smaller content of vagus substances in the ventricles than in the auricles of the mammalian heart. Scherf found in this fact supporting evidence for his conception of the manner in which the vagus affects the formation of stimuli in the ventricle. To be sure, this still fails to explain why the vagus affecting substance, which has been brought to the ventricles by the circulatory pathway, does not have an inotropic effect as well (Rothberger and Scherf).

The reflex origin of extrasystoles has been recognized for a long time. Levy, in particular, was able to generate extrasystoles in this way in cats under chloroform narcosis by means of stimulation of the accelerans. Schott reported heterotopic stimulus formation in poisoned hearts as a result of clamping off the carotids. Schott has collected the extensive literature dealing with cardiac arrhythmias of reflex origin. Among clinical observations in this connection, only the findings of Lennox, Graves and Levine need be mentioned here. These authors found extrasystoles in 70 per cent of patients on a surgical service during operations on the head or neck, whereas during operations on other parts of the body extrasystoles were observed in only 40 per cent of the patients. They concluded from this that vagus stimulation was responsible for the increased occurrence of arrhythmias during operations on the neck.

Beyond the mere idea that the extracardiac nerves are effective in the development of extrasystoles, it has recently been possible actually to produce extrasystoles by central stimulation. Brow, Long and Beattie were able to produce extrasystoles by stimulation of the central vagus stump in cats

which had been narcotized by means of chloroform, and they further succeeded in causing cessation of the extrasystoles by means of a properly directed incision in the hypothalamic region. This "extrasystole center" must of necessity have lain above the "Sherrington level." Dikshit took up the experiments of Brow, Long and Beattie, and investigated the effect of substances injected into the ventricles of the brain on the production of extrasystoles. In this way heterotopic stimulus formation was inaugurated by means of the injection of acetylcholine into the lateral ventricle or into the third ventricle in the cat. Since both vagi were cut, transmission of the stimulus via the sympathetic was assumed. Caffeine and nicotine were found to have a quite similar effect. In several different experiments, no elevation of blood pressure, which may in itself cause extrasystoles, was observed. It was further possible to demonstrate the central origin of the extrasystoles, in that it was consistently possible to cause the extrasystoles to disappear very promptly by means of the intravenous or intraventricular injection of barbital. Dikshit further assumes that the stimulating substances exercise their effect on hypothalamic centers.

The effect of strophanthin when injected into the ventricles of the brain in dogs was investigated by Korth, Marx and Weinstein. The animals were trephined in a preliminary operation and it was possible to conduct the actual experiments without narcosis. This was important because in this way the observations could be carried out on the completely intact heart without previous sensitization. It was apparent that the strophanthin had exercised an extremely strong central stimulatory effect. The electrocardiographic tracings regularly showed a constant and very characteristic picture: a few minutes after the injection there developed first a sinus tachycardia, soon ventricular extrasystoles appeared, which quickly became preponderant and finally led to a true ventricular tachycardia with a rate of about 300 per minute. Thus, strophanthin, when given intraventricularly, causes a violent heterotopic formation of stimuli in tertiary centers. By means of intravenous administration of barbital, it was possible at once to cut short the ventricular tachycardia. Since the tachycardia could be maintained even after section of the vagus, it may be said that the transmission of stimuli is possible by way of both the sympathetic and the vagus. It is very difficult, or indeed impossible, to distinguish between a vagal and a sympathetic effect (Wirkweise). (Scherf has pointed out the problems involved in the investigation of vagal and sympathetic effect on the origin of extrasystoles.) In addition to the above experiment, the effect of other highly active substances (histamine, acetylcholine, thyroxin, etc.) was investigated. It was found that the effect of strophanthin was distinctly different from that of the other substances tried. It may be mentioned here that, as a result of the experiments of Korth, Marx and Weinberg, there must be ascribed to strophanthin a specific effect in increasing cardiac activity by way of the central nervous system. The recognition of this fact would seem to be important for the understanding of the therapeutic effect of digitalis.

In consideration of all these facts, we are able to say that the possibility of the origin of ventricular extrasystoles on the basis of a stimulation of nerve centers in the brain has been experimentally demonstrated. The vegetative nervous system is primarily to be considered as the transmitting organ of the central stimulus.

We wish to report herewith a clinical observation on a patient with softening of the left cerebellar hemisphere, which furthers the hypothesis of a central nervous origin of ventricular extrasystoles.

Case Report

A 58 year old coal dealer, J. G., came under our care March 8, 1937 with the following history: Three weeks previously he had suddenly been taken ill while doing gymnastic exercises. He felt a "tearing sensation" in the region of his heart. Immediately thereafter there were mild pressing sensations in the precordial region which, however, disappeared after a few days. Nevertheless, shortness of breath developed on mild physical exertion, often accompanied by sweating and vomiting. Further, dyspnea, though less severe, also occurred during the night so that the patient had to sit up for a few minutes. Ten days before his entrance to the clinic his physician had diagnosed a mild cardiac weakness and advised treatment in the clinic.

The patient gave a history of severe diphtheria in childhood. He had had diphtheria again as a soldier at the age of 20, for which he was kept in the hospital for five weeks. Nothing was known of any other previous illnesses.

The examination showed enlargement of the heart, especially to the left, confirmed roentgenologically. On fluoroscopy the left auricle also appeared enlarged and small calcifications could be demonstrated in the mitral valve. The heart sounds were faint and no murmurs could be definitely heard. The pulse was absolutely irregular and the electrocardiogram showed auricular fibrillation. There was no edema, the liver was not swollen and percussion and auscultation of the lungs were negative. A diagnosis of mitral disease was made. Under strict dietary treatment the patient had a marked diuresis. He received verodigen from March 13 to March 20, corresponding to a total dosage of 2 grams of digitalis leaves. He felt distinctly better and was allowed to be up out of bed occasionally. The blood Wassermann reaction was negative. The systolic blood pressure varied between 110 and 125. On March 21, which was the fourteenth day of his illness, in the morning he suddenly complained of violent dizziness. He was found lying in bed, groaning and covered with a cold sweat. The patient was completely conscious and remained so. He said that after his bath he suddenly felt very sick, after which there was a sudden attack of severe vertigo so that he was able to reach his bed only with difficulty.

The examination showed the following findings: The color of the patient's face changed frequently and suddenly: marked redness with plainly perceptible warmth of the skin was followed by equally abrupt pallor. At short intervals beads of cold sweat appeared on his forehead and cheeks. The fingers of both hands occasionally showed a cyanotic bluish color and felt cold. He could not sit up in bed. A few minutes later it was observed that the left half of his face drooped. The folds of the face on the left side were smoothed out in comparison with the right. In addition, the patient complained of recurrent attacks of nausea. However, he did not vomit. The blood pressure remained unaltered. The tendon reflexes in his arms and legs were diminished, but equally strong on both sides, and pyramidal tract signs were not demonstrable. The pupils reacted normally to light and convergence. There was no nystagmus. There was no dysphagia.

Particularly striking was a noticeable irregularity of the pulse. While even the day before his pulse had been almost regular, even with the continuing auricular fibrillation, now suddenly numerous, or indeed showers of extrasystoles could be heard over the heart. The size of the heart was unchanged on percussion. The patient was given atropine 0.001 gm. subcutaneously. About ½ hour after the injection and an hour after the onset of the grave clinical picture the pulse again became more regular. The following day no extrasystoles could be noted. On the next day the patient failed noticeably. The marked vasomotor phenomena had ceased, to be sure, and only the vertigo persisted, and to a lesser degree than before. The patient died on the evening of March 22.

The autopsy revealed an embolus at the origin of the basilar artery and acute pale softening of the left cerebellar hemisphere. The mitral valve was markedly stenosed as the result of an old endocarditis, with scarring of the external papillary muscle. The left auricle was markedly dilated and hypertrophied. It could be assumed, accordingly, that the embolus in the cerebral artery had its origin in the left auricle.

In figure 1 we have placed together several different electrocardiographic tracings of this patient. The first tracing represents the electrocardiogram

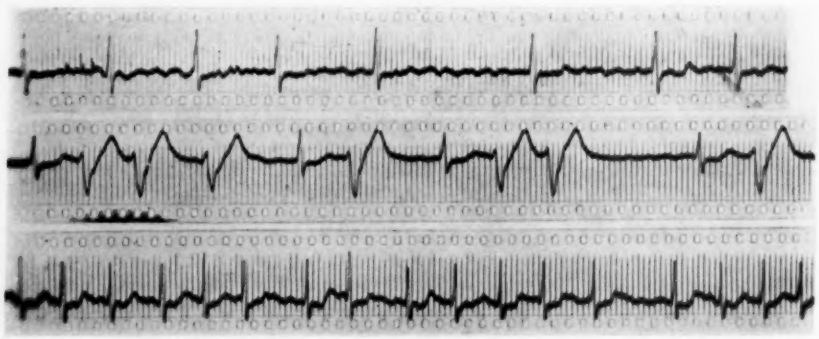

FIG. 1.

Top tracing: March 19, before the attack.
Middle tracing: March 21, ½ hour after the attack.
Lower tracing: March 22, the day after the attack.

of March 19, the day before the apoplectic insult. Auricular fibrillation is apparent. The effect of the digitalis medication is seen in the reduction of the ventricular rate to about 60 per minute. The interval cannot be definitely determined because of the fibrillary arrhythmia. The second tracing is from the electrocardiogram of March 21, about one-half hour after the onset of the attack. Numerous ventricular extrasystoles, which occur in approximate alternation with normal beats, are apparent. In no instance do two normally conducted ventricular beats follow one another, giving the picture of bigeminy. The rate of the conducted beats shows no essential change from that of the preceding day. At least, no demonstrable tachycardia has developed. A rather long interval between an extrasystole and the next normally transmitted ventricular beat is evident. In the bottom

tracing we have finally the electrocardiogram of March 22. The extrasystoles have completely disappeared. The ventricular rate has meanwhile risen to approximately 140.

Thus in this case, in the course of an apoplectic insult affecting the left cerebellum, there suddenly developed showers of extrasystoles. The unusually marked vasomotor phenomena with simultaneous facial paralysis give rise to the presumption that medullary centers were sympathetically involved by the acute softening. We were unable to find any simpler and more obvious explanation of the extrasystoles than the supposition of a stimulating effect on the bulbar vagal center. In favor of this is also the fact that the extrasystoles were easily suppressible by means of atropine. We particularly wish to emphasize that the patient was fully conscious both during the insult and later, that the blood pressure remained unchanged and that there were no signs of circulatory failure.

It is further important to an understanding of these extrasystoles to note that the patient had received a total of 1.9 gm. of digitalis during the days preceding the onset of the insult. Just as in the case of the experimental extrasystoles produced reflexly by the cardiac nerves, previous intoxication of the heart was necessary, so in our case the digitalis treatment provided the necessary "sensitization" of the heart muscle. In the presence of an already existent readiness for heterotopic stimulus formation, the vagal stimulus resulting from the insult led to this manifestation of the heterotopy. Our observation presents a clear analogy to the paradoxical effect of a vagal stimulus on the formation of stimuli in the heart poisoned by aconitin as observed by Scherf. Even though the normal stimulus-inhibitory effect of the vagus on the sinus node is not demonstrable in our patient because of the auricular fibrillation, nevertheless we may assume a negative dromotropic effect of the vagal stimulus on the atrioventricular stimulus conduction. To be sure, it must be noted in this connection that the digitalization had already in any case led to a clearly evident retardation of ventricular activity, but during the insult the rate of conducted impulses is rather lowered than otherwise, or at any rate not increased. Quite in opposition to this is the extraordinarily increased stimulus formation in a tertiary center.

The foregoing observation may, I hope, serve to inspire greater attention to the occurrence of extrasystoles during cerebral affections. We may probably assume that such heterotopies are more frequent than might at first be suspected. Besides the considerable theoretical interest which the "central extrasystole" may claim, there is its practical significance. It may well be that, as Lucke has indicated, centrally produced disturbances in cardiac rhythm sympathetically involve the performances of the heart and that an affection of the heart of central origin is of essential prognostic significance in a primary cerebral disease.

SUMMARY

A brief review is given of our present knowledge of the possibility and the manner of origin of reflex and centrally originated extrasystoles. In this connection is presented the discussion of a clinical observation concerning the sudden occurrence of ventricular extrasystoles in a 58 year old man during an apoplectic insult with softening of the left half of the cerebellum. It is hypothesized that in this case the extrasystoles were originated centrally by means of a stimulatory effect on the medullary vagal nucleus. Finally attention is directed to the theoretical and practical significance of central extrasystoles.

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AN ARTICLE CONTRIBUTED TO AN ANNIVERSARY VOLUME IN HONOR OF DOCTOR JOSEPH HERSEY PRATT

THE IMPORTANCE OF EMBOLISM AS A COMPLICATION OF CARDIAC INFARCTION *

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THE effect of sudden, non-fatal occlusion of one of the larger branches of a coronary artery is well known. The result, in brief, is the formation of an ischemic infarct involving that portion of the heart muscle supplied by the obstructed vessel, the so-called *myomalacia cordis*. The extent of this process depends on various factors, the more important being the size of the occluded vessel and the extent of development of vascular channels capable of taking part in the formation of a collateral circulation. The variability of the process is of practical importance at the bedside because certain clinical features are directly dependent on the presence of certain pathological changes. If the necrosis of the affected area of heart muscle does not involve the pericardium, localized pericarditis, a valuable clinical sign, does not develop. If the necrosis does not involve the endocardium lining the infarcted area, mural thrombi do not develop and secondary embolism, at least from this source, does not occur. It is well known that the necrotic process much more frequently involves the endocardial than the pericardial surface of the infarcted area. Wolff and White [1] state that mural thrombi almost always develop over the infarct. The valuable study of Meakins and Eakin [2] shows, however, that this statement is probably too sweeping, as mural thrombi occurred in only 46.7 per cent of their 62 autopsies. It is important to realize that, on account of the frequency with which the left descending branch is involved, both ventricles are frequently the site of mural thrombi, although Meakins and Eakin's figures indicate that they are about twice as common on the left as on the right side. It is clear, however, that in many patients who have suffered an occlusion there is an opportunity for the detachment of emboli from both ventricles and for their lodgment both in the pulmonary and the systemic circulations.

There is no doubt that some of the earlier writers on coronary occlusion failed to realize the importance of embolism as a complication of the resulting infarction. Other observers noted its occurrence and commented on it. Thayer [3] in his article of 1923 clearly recognized the importance of the condition and diagnosed it during life. Gordinier,[4] in his report on a series of 13 cases published in 1924, suggests that the sudden arterial plugging of the vessels of the brain, viscera or extremities indicates involvement of a branch of the left coronary, while signs of pulmonary infarct suggest involvement of the right coronary or its branches. Hamman,[5] in 1927, ap-

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pears to have been the first to specially emphasize the significance of embolic phenomena, particularly in diagnosis, and since his article numerous authors, including Allan,[6] Harrington and Wright [7] and Parkinson and Bedford [8] have stressed their importance.

As might be expected, there is a decided difference between the figures covering the frequency of embolism based on postmortem examinations and those covering emboli diagnosed by clinical observation.

TABLE I

Site of Emboli as Shown by Autopsy

Author	No. of Autopsies	Lung	Brain	Kidney	Spleen	Limb Vessels	Aorta	Mesenteric Artery
Meakins and Eakin	62	47	4	14	9	11	2	
Parkinson and Bedford	83	7	1	9	8	2	1	3
Wolff and White	19		2	6	2			1
Total	164	54	7	29	19	13	3	4

Table 1, covering 164 autopsies, shows that 130 emboli were discovered in the organs of the 164 subjects. This does not mean, however, that 130 out of 164 *patients* had emboli, because multiple emboli in the same patient are by no means rare. Table 2, covering 945 patients observed clinically,

TABLE II

Number of Patients with Clinically Detectable Emboli

Author	No. of Patients	No. of Patients Showing Emboli
Anderson [9]	9	1
Blumer	175	27
Conner and Holt [10]	287	42
Gordinier	13	3
Howard [11]	165	17
Hyman and Parsonnet	51	17
Levine	145	17
Parkinson and Bedford	100	8
Total	945	132 = 13.9%

shows that 132 or 13.9 per cent had embolic manifestations recognizable during life. Inasmuch as many small emboli fail to give rise to recognizable clinical phenomena and even fairly large emboli may be clinically latent, it seems certain that many more than 13.9 per cent of patients with coronary occlusion have embolism. However, it cannot be assumed that the clinical phenomena resulting from arterial occlusion in the brain, viscera or extremities are all of embolic origin. Some of them are doubtless due, as Meakins and Eakin point out, to thrombosis occurring coincident with or

subsequent to the coronary thrombosis. Owing to the difficulty of deciding, even on the autopsy table, whether a given lesion is thrombotic or embolic, exact figures as to the relative frequence of the two lesions are impossible to obtain, and, as a matter of fact, the decision is of academic rather than clinical interest.

A knowledge of the organs most frequently the *site* of embolism is of practical importance. Table 1, based on autopsy material, shows that the lungs are most frequently involved, followed by the kidneys, the spleen, the peripheral vessels, the brain, the mesenteric vessels and the aorta. Table 3,

TABLE III

Site of Emboli as Observed Clinically

Author	No. of Emboli	Lung	Brain	Kidney	Spleen	Extremity	Periphery	Aorta
Blumer	35	16	9	1		6	3	
Gordinier	4	2	1	1				
Howard	17	9	3	2		2	1	
Levine	17	5	7	1	1		2	1
Parkinson and Bedford	8	3	3	1	1			
Total	81	35	23	6	2	8	6	1

based on 81 collected clinical cases, shows that clinically also the lungs are most frequently involved, followed by the central nervous system, the vessels of the extremities, the kidney and surface vessels, the spleen and the aorta. It is obvious that pulmonary and cerebral emboli would be those most likely to be clinically recognized because they so frequently lead to obvious symptoms and detectable clinical signs. The same is true of occlusion of the arteries of the extremities, which usually causes readily recognizable and characteristic changes. Small emboli in the spleen and kidney could be much more readily overlooked, especially in patients so seriously ill as many of these patients are.

The *period* in the disease at which emboli are likely to occur varies within wide limits. In a collection of 40 patients with emboli observed by the author or taken from Levine's series [12] just 60 per cent showed evidences of embolism within 10 days of the occlusion. The remaining 40 per cent showed embolic phenomena between the eleventh and the thirty-eighth day. In some instances embolism occurred almost simultaneously with the coronary lesion, but this took place in only two out of 40 patients and it is possible that the lesions were thrombotic rather than embolic. Embolism on the second day is not uncommon; one such case seen by the writer occurred when the patient was unfortunately upset while being carried upstairs in a chair. The largest number of embolic phenomena occurred from the seventh to the tenth day. The number of cases with definite information as to the time of embolism is, obviously, much too small for accurate statistical purposes and these figures must be regarded as merely suggestive.

The *clinical manifestations* of embolism in these patients were the usual ones. In the pulmonary cases sudden pain in the chest, hemoptysis, cyanosis, shock and physical signs of local pulmonary change were usually present. In the cerebral cases the picture varied with the localization of the lesion; partial or complete hemiplegia, with or without aphasia, being the most common lesion in the severer cases. In some patients minor effects such as ptosis of one eyelid, visual hallucinations, strabismus or temporary amblyopia were observed. The involvement of peripheral vessels, almost always in the lower extremities, constituted a serious problem when it occurred. Gangrene commonly resulted and frequently the condition of the patient was so poor that active surgical intervention could not be seriously considered and, on account of very low blood pressure, the use of vasodilators was hazardous. Involvement of the skin vessels was seen occasionally, resulting in superficial areas of gangrene. Sudden attacks of local peripheral pain, without obvious signs, were present in one of my patients.

There is a small group of cases which require special consideration, i.e. those in whom embolic phenomena occurred months or even years after the coronary occlusion.* One patient, personally observed, had a cerebral accident, presumably an embolism, a year after the occlusion. In one of Levine's patients a left hemiplegia developed eight months after the occlusion. Hyman and Parsonnet[13] cite two patients who died of cerebral embolism, one three years and one five years after a coronary occlusion. One can hardly assume, I think, that the emboli in these patients originated in a mural thrombus which developed over the infarcted area at the time of the attack, for the fact that these patients recovered from the attack made it probable that these thrombi became organized and harmless as a source of emboli. It is possible, but not probable in view of the usual postmortem findings in healed infarction, that thrombosis is more likely to develop at the site of a former infarction than elsewhere, even years after the original lesion. It is more likely, perhaps, that the emboli in these patients had their origin in intracardiac thrombi developing elsewhere in the heart as a result of poor circulation, just as they not infrequently develop in apparently well compensated cases of mitral stenosis. The question cannot be conclusively decided without more postmortem evidence.

The most important bearing which the question of embolism following cardiac infarction has is its influence on *prognosis*. It is certainly true that many of these patients recover from pulmonary infarcts but, as McNee[14] has shown, the detachment of pulmonary emboli large enough to cause death may occur. Furthermore, there can be little question that the added strain associated with the development of one or more pulmonary infarcts may prove too severe a burden on the damaged heart. In my limited experience the development of cerebral embolism during the acute phase of cardiac

* These cases are not included in table 3.

infarction has usually resulted disastrously. Recovery after late cerebral emboli may undoubtedly occur. Embolism of the larger vessels of the limbs has a most serious effect on the prognosis, for the impaired circulation and the low blood pressure encourage the development of gangrene and the outcome is commonly a fatal one.

So far as *treatment* is concerned, it would seem that the frequency with which mural thrombi are present in coronary occlusion serves to emphasize the necessity for prolonged and absolute rest during the acute phases of the process. It also justifies the attitude of many clinicians regarding the avoidance of medication with digitalis, unless there is some very definite indication for its use, such as auricular fibrillation.

The following conclusions seem justifiable:

1. In patients with cardiac infarction due to coronary occlusion mural thrombi are present over the endocardial surface of the infarcted area in about 50 per cent.

2. These mural thrombi may be limited to one cavity, but are frequently present in both the right and the left side of the heart.

3. Fragments of such thrombi are detached and produce clinically recognizable embolic phenomena in about 14 per cent of patients with cardiac infarction.

4. Embolism is most likely to occur during the first 10 days following a coronary occlusion.

5. Embolism of branches of the pulmonary artery is the most frequent type, but is less serious prognostically than cerebral embolism and embolism of the larger vessels of the extremities.

6. The frequency of such emboli emphasizes the importance of absolute and protracted rest and the avoidance of medication by digitalis, unless especially indicated, in the treatment of cardiac infarction.

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AN ARTICLE CONTRIBUTED TO AN ANNIVERSARY VOLUME IN HONOR OF DOCTOR JOSEPH HERSEY PRATT

KAPOK AND MOLDS: AN IMPORTANT COMBINATION *

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IN a former study of kapok ("silk floss") we [1] showed that a considerable number of patients with asthma have been relieved of their symptoms simply by eliminating kapok from the environment. We pointed out that the fibers of new kapok, freshly removed from the pod, have a high luster and resiliency; that extracts of them rarely give skin tests; that this kapok fresh and new, does little harm. Old kapok, however, which has been used as the stuffing of pillows, mattresses, and furniture, for some time, has a dull appearance. The fibers are dry and brittle, and readily break down into a fine dust. Extracts of old kapok give positive skin tests in many patients and the dust of old kapok is a frequent cause of asthma and other allergic disorders. The new and the old material have physical and chemical properties which are quite different and the content of the skin active principle appears to run parallel with the other properties.

What causes these changes due apparently to "age" in kapok? Van Leeuwen [2] believed that fungi were the causative agents. He observed that *Aspergillus fumigatus* which had been isolated from old kapok and which in itself gave negative reacting extracts, was able to convert non-reactive kapok into reactive kapok if it was allowed to grow on the non-active material. On the other hand, G. T. Brown [3] in his recent studies on the importance of molds to allergy was unable to demonstrate any changes occurring in sterilized kapok after its inoculation with cultures of molds and other microorganisms including various species of *alternaria, aspergilli,* and *mucor.*

The observations of Cohen [4] and his fellow workers with raw cotton suggest that other factors can be responsible. They found that non-reactive cotton which had been sterilized and kept sealed for several months became reactive. The changes had taken place in the absence of viable microorganisms, and moreover, as the materials were in sealed containers, it is doubtful whether other external factors such as oxygen or carbon dioxide could have been important in bringing about the changes observed. The evidence presented was more in favor of internal factors that were thermostable and which perhaps possessed properties similar to those found in enzymes.

These previous observations have not explained the clinical findings.

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There is need for additional studies, and in this present work, we have endeavored to investigate a few of the factors which we believed were important in the case of kapok.

Experimental

At the outset it was necessary to ascertain what effect sterilization by heat might have on the skin active principles of the various materials that would be used in the work. Suitable quantities of old kapok, old cotton linters, and of house dust, were sterilized for three hours at a pressure of 15 pounds per square inch. After cooling, each substance was extracted with Coca's solution and each extract was tested in the skin of seven patients. The skin tests with the extracts of the sterilized materials gave results which were in every case identical with the results of skin tests with extracts of the original unsterilized materials. Thus, whatever the skin active principle in old kapok, in old cotton linters, and in house dust may be, it is not affected by ordinary sterilization.

A second experiment was designed to study the effect of time alone on sterilized material. Cohen's experiment was repeated. Samples of kapok fiber obtained from the fresh opened pod were placed in large vials which were then sealed with rubber caps and sterilized for three hours in the autoclave. To equalize the inside and outside pressure of the vial during sterilization, a hypodermic needle plunged through the cap was used as a vent. At the end of sterilization, the needle was removed and the vials further sealed with melted paraffin. At this stage, the fibers as seen through the glass of the vial appeared to have lost some of their luster and to have darkened in color. The vials of sterilized new kapok were then placed as follows: One was set upon the window ledge so as to be exposed to the sunlight. Another was placed in a covered box that was put in a laboratory drawer. As a control for any possible changes occurring due to temperature, a third vial was placed in the rear of the laboratory ice box. All vials were left undisturbed for a period of six months. At the end of this time, the materials within the vials were removed, weighed, and extracted with Coca's solution on an equal weight volume basis. They were sterilized by Seitz filtration. All the extracts appeared alike and no visible difference could be noted between them and other extracts of freshly isolated pod kapok. Skin tests with the three extracts were made in 18 subjects who were known to give good skin reactions to old kapok but the results were entirely negative. Moreover, these same tests were repeated in 14 of the 18 subjects and again gave the same negative results. We thereby concluded that, at least within a period of six months, no significant changes had occurred in sterilized and sealed pod kapok whether it was exposed to sunlight, protected from light, or kept at temperatures of 8°, or at ordinary room temperature.

In a third experiment, the effect of dryness was investigated. A mode-

rate quantity of sterilized pod kapok was placed in desiccators over calcium chloride and over concentrated sulphuric acid. These likewise remained undisturbed for six months after which time the kapok was removed and extracted at once and taken to the clinic for testing purposes. In a series of 10 old kapok sensitive individuals, all extracts of the dried kapok gave negative results in all instances. Apparently prolonged exposure to a dry atmosphere does not cause any appreciable change in the skin reactivity of new kapok. If loss of moisture is the cause of breakdown in the kapok fiber, it alone is not the cause of the development of skin reacting factors.

At this point in the study, the supply of pod kapok gave out. (We were informed that the Dutch Government has prohibited the shipment of kapok pods and seeds from its colonial possessions.) We were forced to be content with the use of new kapok from a freshly opened bale.* This material, while not as inactive as the pod material so far as skin tests were concerned, was distinctly less reactive than old kapok.

In a fourth experiment, we sought to rule out the possible effect of oxygenation and carbon dioxide action. We reasoned that if either of these processes was important to the changes, an increased concentration might speed up the reactions so that their effects could be observed within a comparatively short time. To study this matter, three large florence flasks were half filled with bale kapok and sterilized for three hours in the autoclave. After this treatment, we observed as before that gross changes similar to those mentioned in the case of pod kapok were present. The fibers had less luster and were of a darker shade of yellow. The flasks were allowed to cool over night and the next morning they were fitted with sterilized stoppers and tubing so that the atmosphere within the flasks could be easily changed. Into one of the flasks, cotton filtered oxygen was allowed to pass for a period of 15 minutes. The oxygen supply was then shut off and the feeding and exit tubes clamped tightly. In similar fashion, the atmosphere in the second flask was changed to carbon dioxide. The third flask was left sealed and served as a control. Thereafter, over a period of three months and at intervals of every three days, the oxygen and carbon dioxide in the first two flasks were renewed by the same technic. Meanwhile the flasks were kept at room temperature. At the end of three months, the material in each of the three flasks showed no changes in the gross appearances. It was removed and extracted. The three extracts were adjusted to an equal weight volume basis and were tested in 14 sensitive subjects. In all cases, it was impossible to distinguish any difference in the skin tests between the extracts of the material which had been exposed to either oxygen or carbon dioxide and that of the control. The evidence would indicate that the presence of concentrated oxygen or carbon dioxide alone over a prolonged period of time was not an important factor in activating relatively inert new kapok.

* The material was obtained through the courtesy of the Kapo Products Company.

In a supplementary experiment and with the purpose of additional control, oxygen and carbon dioxide respectively, were bubbled at rapid rates through extracts of old and new kapok for periods of two to eight hours. Skin tests with extracts treated in this manner gave results that were comparable in all respects with the untreated extracts. Apparently the skin active principle in kapok extracts is not easily, if at all, affected by continuous contact with pure oxygen or with pure carbon dioxide.

Meanwhile, other investigations of the possible effects of microorganisms were in progress. Extracts of the pure cultures of the common molds isolated from old kapok and described in a previous paper by Conant and the writers[5] were tested on a group of 54 old-kapok-sensitive individuals. Ten patients gave moderately positive reactions with the extract of chaetomium species; nine with the extract of *Aspergillus niger;* nine with the extract of penicillium species; and seven with the extract of *Rhizopus nigricans.* These results are comparable to those of Brown[3] and of Feinberg[6] both of whom have tested large groups of allergic patients with extracts of the more common molds.

So far then, it has been demonstrated, first that extracts of new, unused, and freshly obtained kapok give negative skin tests; that this new material may be held in the laboratory under various conditions for considerable periods of time and still its extracts will give negative tests. Second, that extracts of the cultures of molds readily isolated from old used kapok gave positive skin tests in only a few of the old-kapok-sensitive patients.

Evidently, the many positive skin tests obtained with old kapok extracts depended neither upon the substance itself—the kapok fiber, nor upon the molds themselves that might grow in it. Perhaps, however, they depended upon the combination of molds plus kapok; that certain molds growing on this particular substrate would cause chemical changes which would result in the development of skin reactive principles.

To test this idea, the following series of experiments were carried out:

From Professor Weston we learned that certain molds have a predilection for certain substrates; that even in a single species, different individuals may have habits of growth which are quite different, one from another; and therefore, that it is important in any inoculation experiment, to use those strains which there is reason to think might grow well on the particular substrate. The idea of obtaining the inoculum by washing the old used material and using all the organisms obtained in the sediment was developed.

The procedure employed was as follows: Generous samples of the various old materials—old kapok, old cotton linters, and house dust—were wet down well with sterile salt solution (0.9 per cent) and the mixtures were allowed to stand and extract for approximately one hour. Then, the materials were stirred vigorously. The mass was squeezed in gauze and the dirty fluid was collected in a sterile container. The sediments were separated by centrifuging at high speed, adding increments of 40 c.c. of the fluid until a

sufficient amount of sediment had been secured. The supernatant fluids which contained extracts of old kapok, of old cotton linters, or of house dust, were discarded, but when later the sediments were washed in three changes of salt solution, the washings were saved and pooled for control purposes. The washed sediments were suspended in sterile distilled water and transferred to sterile atomizers from which they were sprayed in liberal quantities into flasks containing the substrate. These flasks were prepared in this way: Liberal quantities of kapok fiber from the bale, cotton fibers from new unopened bolls,* and finally, the fibers of commercial non-absorbent cotton, were finely cut with scissors, placed in florence flasks, sterilized in the autoclave, and finally spray inoculated. After inoculation with the spray, the mouths of the flasks were covered with inverted beakers and placed in large tin cans that were fitted with tight covers. To secure a high degree of humidity, the lower portions of each can were packed with moistened sphagnum moss. The relative humidity within the cans was checked at frequent intervals through two small holes in the covers and was always found to be above 80 per cent. In this experiment, all flasks were prepared in duplicate, and to eliminate the possibility of cross contamination, separate cans were used for each inoculum and its set of substrates. The cans were kept in the laboratory at ordinary room temperature. At the end of 60 days, one flask of each duplicate set was removed from the cans; the other flask being taken out after 120 days. Grossly, most of the flasks showed evidence of the growth of molds among the fibers—a few colonies black, yellow, green, or gray were seen here and there and more of them in the 120 day flasks, but the growth was not uniform or constant for any one sediment-inoculum or any one substrate. The heaviest growth seemed to be in the flask containing boll cotton which had been inoculated with old cotton-linter sediment, thus supporting the suggestion of Dr. Weston that certain molds have a predilection for certain substrates. Non-absorbent cotton seemed unable to support a growth of molds, for none of the flasks containing this material showed any gross change even after standing in the moist chamber for 120 days—and this was regardless of which particular inoculum was used. At the end of 60 days, the material in the first set of flasks was extracted by adding Coca's buffered phosphate solution to it and allowing the mixture to stand over night. The extracts were adjusted on a uniform weight-volume basis and were filtered first through paper and then through a Seitz wafer. At the end of 120 days, the second flask of each set was removed, examined, and extracted in the same manner.

Skin tests with the extracts were made as soon as they were prepared. Controls were provided as follows: Similar flasks of the vegetable fiber substrates were inoculated with mixtures of known mold cultures while others were inoculated with a bacterium—*B. subtilis* being chosen. Another set of flasks was placed in the moist chambers without any inoculation.

* The cotton bolls were obtained through the courtesy of The Murray Company, Dallas, Texas.

The sediment inocula were tested separately to see whether they alone might give skin tests. The washings of these sediments were pooled and saved as described, but skin tests with them were always negative. Each of the sediment suspensions was planted on duplicate dextrose agar slants, one set being incubated for 48 hours and the other for one week. At the end of these incubation periods, the whole cultures were extracted with Coca's buffered saline and the extracts passed through sterile Seitz filters. Skin tests with each extract gave negative reactions in a group of kapok-house dust-cotton linter-sensitive subjects.

TABLE I

Skin tests with extracts of bale kapok, boll cotton, and non-absorbent cotton which had been sterilized first and then inoculated with dust sediments and microörganisms. Test subjects all skin sensitive to old kapok

Subject	60 day Extracts																	
	Inoculum:																	
	Kapok Sed.			Linter Sed.			Dust Sed.			Mold Mixt.			*B. Subtilis*			Controls		
	B.K.	B.C.	N.C.	B.K.	B.C.	N.C.	B.K.	B.C.	N.C.	B.K.	B.C.	N.C.	B.K.	B.C.	N.C.	B.K.	B.C.	N.C.
1	0	0	±	±	++	0	±	±	0	0	0	±	0	0	0	0	0	0
2	0	±	0	±	++	±	±	0	0	0	0	0	0	0	0	0	0	0
3	±	±	0	±	++	±	±	±	0	±	+	0	0	0	0	0	0	0
4	0	0	0	+	++	0	0	0	0	0	0	0	0	0	0	±	±	0
5	±	±	0	0	0	0	0	0	0	±	+	+	0	0	0	0	0	0
6	0	±	0	0	+	0	0	0	0	0	0	0	+	0	0	0	0	0

Subject	120 day Extracts																	
	Inoculum:																	
	Kapok Sed.			Linter Sed.			Dust Sed.			Mold Mixt.			*B. Subtilis*			Controls		
	B.K.	B.C.	N.C.	B.K.	B.C.	N.C.	B.K.	B.C.	N.C.	B.K.	B.C.	N.C.	B.K.	B.C.	N.C.	B.K.	B.C.	N.C.
1	+	0	0	0	++	0	0	0	0	+	+	0	0	0	0	0	0	0
2	±	+	0	+	0	0	0	+	+	0	0	+	0	0	0	+	0	0
3	+	+	0	+	++	0	+	+	0	0	0	0	±	+	0	0	0	0
4	0	0	0	+	++	0	0	+	0	+	0	+	+	+	0	0	0	0
5	+	+	0	+	++	±	+	+	0	0	+	0	+	+	+	0	0	0
6	0	0	+	0	0	0	+	0	0	+	0	0	0	0	+	0	+	0
7	+	+	0	+	++	0	+	+	0	+	0	0	+	0	0	0	0	0

B.K. = Bale kapok. B.C. = Boll cotton. N.C. = Non-absorbent cotton.

The results of skin tests with the extracts of the inoculated flasks are shown in table 1.

These results were not striking with any of the 60 day extracts and for the most part the reactions, where positive, were distinctly less than those given by the extracts of the corresponding old material. The greater frequency of positive reactions with the 120 day extracts is good evidence that the development of the active skin-test principle is associated with the amount of growth. The boll-cotton, cotton-linter sediment combination which showed the greatest amount of mold growth yielded extracts which gave the greatest number of positive reactions of any of the combinations. The negative reactions with the extracts of the controls indicate that the time element alone is not an important factor in the formation of the active principle.

The results do not show any relationship between the three inocula. Boll cotton inoculated with each of three sediments gives different results in each instance. This observation is interesting as the studies of Cohen et al. indicated that the active principles of house dust and old cotton linters had a common source. The negative skin tests with non-absorbent cotton however inoculated also indicates that the principle necessary for the growth of molds is similar to that necessary for the production of skin tests—the principle being removed in the manufacture of non-absorbent cotton.

Sterilized materials yielded only a meager growth after a period of 60 days. This raised the question whether sterilization in itself had affected the materials so that they became less suitable for the growth of molds. To investigate this possibility, the 60 day set of the previous experiment was repeated, using unsterilized materials. Inoculation with the common mold mixture and with the *B. subtilis* culture was omitted in this experiment, the controls being simply the unsterilized, uninoculated material which had been incubated in the same way. When this unsterilized material was inoculated with the mold containing sediments, a marked growth was obtained. Not only were there isolated colonies here and there between the fibers, but the contents of the flasks containing boll cotton and bale kapok all showed a dirty gray color with numerous black and yellow colonies. In contrast, the non-absorbent cotton flasks had no obvious growth and the uninoculated flasks showed no obvious growth.

The results of skin tests with extracts of the flask contents after incubation for 60 days in the moist chamber are shown in table 2. The results here are quite different from those obtained with the sterilized material. As the table shows, skin tests were not only positive but were often well marked. Bale kapok and boll cotton gave positive results in almost all instances and regardless of whether they were inoculated with the sediments obtained from old kapok, from old linters, or from house dust. If left uninoculated, however, the results were negative. This last is surprising because one would suppose that the crude material might contain in itself

molds of various sorts which would develop and produce changes similar to those in the inoculated material. Perhaps the time (60 days) was too short for full development or perhaps the samples obtained even though unsterilized were yet more or less free of the common molds. The former possibility is more likely. It is noted in this experiment also that non-absorbent cotton was not changed by mold growth sufficiently to produce a skin-test active extract.

TABLE II

Skin tests with extracts of bale kapok, boll cotton, and non-absorbent cotton not sterilized but inoculated with various materials. 60 day extracts. Test subjects all skin sensitive to old kapok

Subject	Inoculum:											
	Kapok Sed.			Linter Sed.			Dust Sed.			Controls		
	B.K.	B.C.	N.C.	B.K.	B.C.	N.C.	B.K.	B.C.	N.C.	B.K.	B.C.	N.C.
1	+	+	0	+	++	0	0	+	0	0	0	0
2	++	+	0	++	++	0	++	++	0	0	0	0
3	++	+	0	+ 2	++	2 0	+	+	0	0	0	0
4	0	0	0	+	+	0	0	0	0	0	0	0
5	+	+	0	++	0	0	+	+	0	0	0	0
6	+	+	0	++	++	0	+	+	0	0	+	0
7	0	0	0	+	++	+	0	±	+	±	0	0
8	++	++	0	++	++	0	++	++	0	0	+	0
9	±	+	0	+	++	0	0	+	0	0	0	0

B.K. = Bale kapok. B.C. = Boll cotton. N.C. = Non-absorbent cotton.

These experiments demonstrate that the cause of the breakdown in the kapok fiber as well as the development of the skin test active principles in extracts of old kapok is the growth of molds upon the vegetable substrate. Skin tests with the molds alone are usually negative; skin tests with the kapok itself are negative; but when molds and kapok are combined, positive skin tests became easily demonstrable. The observations explain the clinical experiences previously described and point again to the great clinical importance, that is to say, the danger in the use of old kapok in the home. The same considerations apply to cotton linters. These vegetable fibers support the growth of molds and so develop skin test active principles. Non-absorbent cotton has, in the process of manufacture, lost something which is important for the support of mold growth as well as for the production of skin reactive extracts. Presumably, the same argument will

apply to all untreated fibers of vegetable origin in contrast to those of animal origin—like hair and feathers.

Summary

1. Steam sterilization of vegetable fibers (cotton and kapok) changes the material in some way so that molds will not grow well upon it.

2. Time alone produces no change in kapok fiber which has been sterilized, regardless of whether this time be passed in the light, the dark, or the cold.

3. Drying has no effect in producing the skin-test active principle.

4. Oxygen and carbon dioxide have no effect even though the fibers are kept in the atmosphere of these gases for as long as three months.

5. Molds, however, will cause changes in both boll cotton and bale kapok, especially if the molds are taken from samples of old kapok, old cotton linters and house dust. However, extracts of the inoculum itself give no skin tests.

6. The skin-test active principle is directly proportional to mold growth so that:

7. It is more marked in the 120 day cultures than in the 60 day cultures; and

8. It is much more marked when unsterilized material is inoculated.

9. The experiments demonstrate that the active skin-test principle in commercial kapok depends upon the growth of molds in the kapok (vegetable) fibers.

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AN ARTICLE CONTRIBUTED TO AN ANNIVERSARY VOLUME IN HONOR OF DOCTOR JOSEPH HERSEY PRATT

THE CLASS METHOD IN THE TREATMENT OF ESSENTIAL HYPERTENSION *

By ROBERT W. BUCK, M.D., *Boston, Massachusetts*

WE are able to treat successfully such diseases as syphilis, allergic asthma or congestive heart failure because we have a good deal of accurate knowledge concerning their etiology and pathology; in the case of other conditions such as scurvy, malaria or pernicious anemia the lack of such knowledge did not prevent the discovery of a specific cure. Essential hypertension belongs to a third group of clinical entities, the etiology and pathology of which remain to a considerable extent obscure and for which there is no specific treatment. Fortunately perhaps, our profession has never permitted a deficiency in its knowledge of the exact nature of a disease to stand in the way of its therapeutics, so that there is no lack of suggestions for the care of the patient with hypertension. Ayman [1] collected within a decade over 200 accounts of procedures directed toward the relief of this condition. The remarkable fact is that they were all successful! He analyzed 35 of these articles in some detail, and found that practically every one reported complete or partial symptomatic relief, and in the majority a moderate to marked reduction in blood pressure was reported.

The " good results " obtained are not comparable to the cure of scurvy by the administration of orange juice or the relief of the symptoms of pernicious anemia by liver therapy. They consist in a subjective sense of improvement, the relief of a variety of symptoms, and a fall in the blood pressure level. All these results can be duplicated in patients treated only by suggestion, as Ayman has demonstrated. It does not follow that they are illusory. Such knowledge as we have of the etiology and pathology of hypertension is consistent with the clinically observed improvement which follows a variety of therapeutic measures if we consider that the two factors common to them all are sedation and the prevention or relief of vasoconstriction. Suggestion, by inspiring a sense of confidence as to the benefits of treatment, relieves worry, quiets the patient and permits him to relax. There is no good theoretical reason why suggestion should not thus accomplish sedation and vaso-relaxation as effectively (in kind and perhaps occasionally in degree as well) as luminal, alcohol, the nitrites, watermelon seed extract, mistletoe or surgery of the sympathetic nervous system.

I do not wish to seem to advocate suggestion as a method of stopping the pathological process which results in an arterio-capillary fibrosis or a

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necrotizing arteriolar sclerosis, beyond the point suggested by many literal minded persons that "nervous tension" may possibly play some part in furthering the progress of such lesions. Confining ourselves to the consideration of the mere psychic benefit to the patient, it is pertinent to recall that the symptoms presented by patients with high blood pressure in its early stages are identically those complained of by psychoneurotic patients. Some observers have even concluded that "the early symptoms associated with essential hypertension are of psychic origin." [2]

If we may conclude that sedation and relaxation are the two objectives to be sought in the treatment of our hypertensive patients, we are in a position to cease following the will o' the wisp of specific cure and to settle down to the development of a well planned therapeutic regime. Only thus can we rescue the hypertensive patient from the neglect that he now receives. Our interest in him must not be casual and intermittent, as it now is for the most part, but continuous and purposeful.

A method of demonstrated value in the treatment of the psychoneuroses might be expected to be helpful in relieving the symptoms of hypertension. The success of the "Thought Control" class established by Dr. Joseph H. Pratt [3] at the Boston Dispensary in redeeming a very considerable number of these patients suggested to us that a similar method applied to the treatment of patients with hypertension might be equally valuable.

Certainly the power of suggestion is "stepped up" when the suggestion is administered to a group. When a patient joins a group his individuality merges with it, and his individual resistance to suggestion is overcome by the contagion of the group response to its leader.

Again, the class method is helpful to the members of the group because of the morale which is developed in any association of persons working toward a common end. It is always difficult for the patient to carry out any regime of treatment "on his own." The difficulty is comparable to that of self-instruction in painting or drawing or gymnastics or Latin or mathematics. Class instruction encourages competitive striving for results; it causes the members to try to emulate those who are most successful; it develops a spirit of coöperation and enthusiasm which is possible only in a group with a common objective.

We have for several months conducted a "Hypertension Class" recruited from patients attending the medical clinic at the Boston Dispensary. The only requirement for membership is a high blood pressure. The attendance of patients with advanced renal failure is not encouraged, but neither is it denied them.

Our purpose is to present to these invalids a program of living which will enable them to consistently live at the optimum level of well being which is possible for them. This is in many or perhaps the majority of instances surprisingly high.

The program is built about a threefold approach which can be illustrated

graphically by a triangle each side of which represents one aspect of the treatment. This constitutes the Rule of the class (figure 1) and is demonstrated at each meeting.

By " Medical Care " we mean all treatment available in the clinic apart from participation in the class. This may be medical or surgical and in-

FIG. 1. The Rule of the Class.

cludes such matters as the treatment of varicose veins, or diabetes, sinusitis or congestive heart failure. We make no attempt to supervise or direct this adjuvant treatment, but prefer to permit the patient to attend to the care of his own needs as these are discovered by his regular medical attendant. We simply urge upon him the necessity for his giving ordinary sensible attention to his general health.

The second arm of the triangle, " Diet," is a rather arbitrary affair. To the average patient, a Diet is like Voltaire's God: if It did not exist, he should have to create It. I believe it is more desirable to build upon this hope than to antagonize our patients by denying the importance of a proper dietary. The diet chosen is advised first on the grounds that it may be essentially beneficial. It certainly is not harmful. People who by necessity followed this diet in the Scandinavian countries during the war years are reported to have shown a decreased mortality not only from hypertension but also from other diseases, especially those accompanied by degenerative processes in the cardiovascular system. This diet is that which Hindhede [4] has promulgated for many years. It consists simply of potatoes, baked and eaten with the skins intact, dark bread and butter, milk, and apples or other fresh fruit. The members of the class are permitted to vary this rather Spartan, but on the whole well balanced and certainly economical fare by occasional mild lapses on holidays or when they go out to dinner and do not wish to be thought eccentric. If the diet is adhered to as well as most patients do adhere to it, we need not worry much about calories.

The base of the triangle is in fact the basis of our whole systematic method—the use of suggestion and psychotherapy. In the class this takes

the form first of education and explanation. The relatively benign course of essential hypertension is stressed, a plausible theory of its pathological physiology consistent with the knowledge we have is presented, and the importance of physical and nervous strain in the development of symptoms is emphasized. Abundant material is available here for many lectures, which are received with interest and appreciation, and more, with a feeling of reassurance and often the alleviation of fear.

Further, the psychic origin of the symptoms of early hypertension is explained. Without attempting any individual psychoanalysis, we simply point out over and over again the important rôle of the emotions, of apprehension and worry and unpleasant thoughts in the genesis of symptoms. The field here is too great to discuss within a paragraph. The fact is that all middle aged hypertensives (and many others) need a spiritual director, or call him a psychiatrist, or a personality worker if this seems preferable, and if as physicians we fail to utilize our opportunities in this direction we are not doing justice to our patients.

Finally, at each class meeting, the importance is stressed and the practice insisted upon, of regular and systematic relaxation. We should like to advocate that the " progressive relaxation " of Jacobson [5] be developed and practiced by all of our patients, but the method is too time consuming and instruction in its use requires too much individual attention for it to be practicable. It is possible to obtain results with a less elaborate technic. We have a five minute relaxation period at each meeting during which all persons in the room are asked to individually follow the demonstration by the leader. Here again, it is difficult to convey briefly the really profound effect which can be attained by the proper conduct of this five minute period of complete silence and repose. The class members practice their " relaxation exercise " once, twice or three times daily, if they are able, during the week.

A feature which is important, and never omitted, is the giving of " testimony " by the older members. The success of those who have been practicing the tenets of the class is a powerful factor in starting the new members off in the proper spirit of optimism and earnest attention to the rules. Those who have benefited by their attendance are ever willing to stand up and say so to the other members of the group, and their testimony is more effective than any amount of lecturing or grave advice.

Our results over a period of several months have justified our expectations. Patients of course report the relief of such symptoms as dizziness, pain in the neck, hot burning sensations in the head, insomnia, and " shortness of breath." The uniformity with which they report that they " feel fine " (when formerly they presented a variety of symptoms) in itself testifies to a new mental attitude if not to any modification of the underlying pathological process. Some of our patients have shown no striking change in the level of their blood pressures, but in two-thirds of those who have

made three or more visits to the class a fall in pressure of from 18 to 46 millimeters of mercury has been observed.

Our aim is not, however, primarily to reduce blood pressure; it is rather to aid these patients to attain an optimal level of well being. The approach is frankly largely psychologic. We feel that we have accomplished a worth while result if our patients lose their fears, adapt themselves to their condition and become optimists rather than pessimists, and we view our method as an application of well known and well tried principles rather than as a new form of treatment. In the clinic it enables us to utilize these principles far more effectively than they can be used in the individual interview.

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PAROXYSMAL VENTRICULAR TACHYCARDIA: REPORT OF THREE CASES; MECHOLYL USED AND INEFFECTIVE IN TWO *

By NEUTON S. STERN, M.D., F.A.C.P., *Memphis, Tennessee*

THE comparative rarity of paroxysmal ventricular tachycardia, and the opportunity to report upon the ineffective use of mecholyl in proved cases suggested the presentation of these cases.

CASE REPORTS

Case 1. S. B. C., female, single, aged 75, seen in consultation with Dr. Otis S. Warr. She was admitted to the Baptist Memorial Hospital December 25, 1936, for pain in her chest, cough and expectoration. Diagnosis was made of bronchopneumonia and hypertension, the blood pressure being 155 systolic and 110 diastolic on admission. Three days later she became semicomatose, cyanotic, with shallow breathing of the Cheyne-Stokes type. Blood pressure 135 systolic and 85 diastolic. An

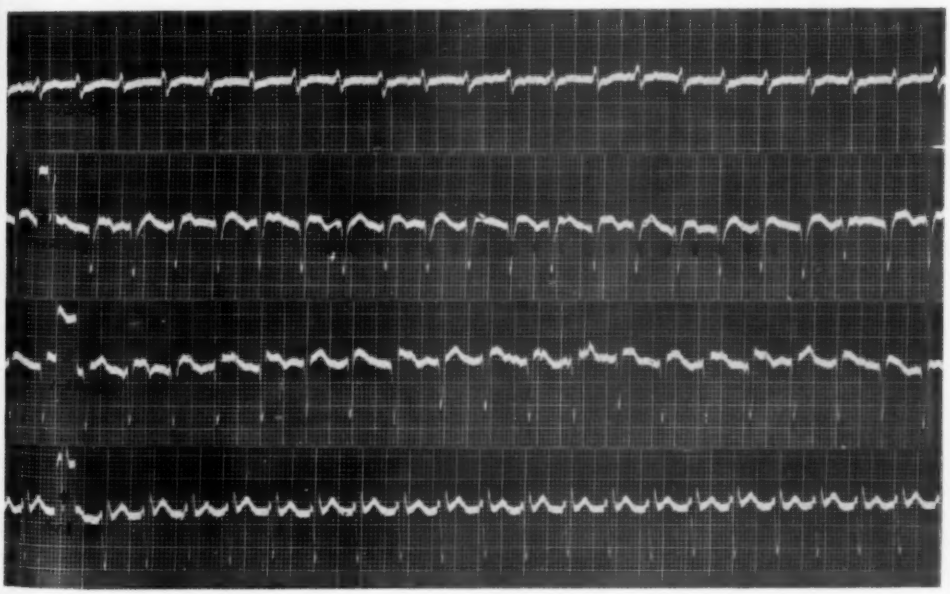

FIG. 1.

oxygen tent was used with relief, and consciousness returned. On the following days the pressure varied from 104 systolic and 80 diastolic to 160 systolic and 108 diastolic, and once to 180 systolic and 90 diastolic. Breathing continued to be somewhat difficult. The findings by roentgen-ray suggested unresolved pneumonia with

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clear areas possibly due to abscesses. The heart rate was rapid but regular, 100 to 120. Roentgen-ray therapy to the chest was tried January 5 and 8, 1937. On January 9, dyspnea increased, and the heart showed a gallop rhythm. The blood pressure tended to stay about 160 for the next few days. Dyspnea, tachypnea and râles in the chest indicated left ventricular failure, and the sudden attack of December 28 with drop of pressure suggested coronary occlusion.

On January 12, an electrocardiogram (figure 1) was made at the bedside. The ventricular rate was rapid, 167, the rhythm was regular, but the complexes showed slight variations in the length and shape of the principal deflections, and considerable

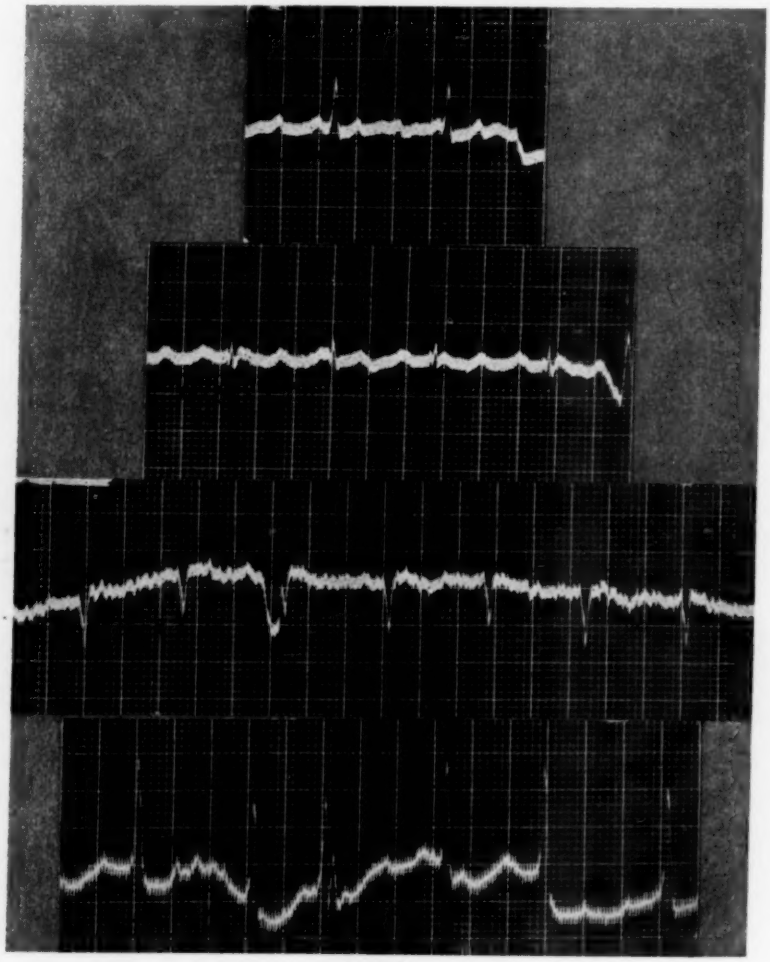

FIG. 2.

variations in the curve between these deflections. These variations were believed due to small P-waves superimposed on the ventricular complexes, falling at different times in the cycles, and were sometimes visible and sometimes buried. On this interpretation the auricular waves seemed to be regular and of a rate of 273. The interpretation of these electrocardiographic findings was: Auricular flutter, complete A–V dissociation, ventricular tachycardia (probably nodal).

A similar curve was obtained on January 13.

On January 14, the ventricular rate was very much slower (115) and the complexes had changed in shape (figure 2). The auricular rate was 286. The diagnosis was made of auricular flutter, with complete heart block. In the light of this evidence it was believed that the rapid ventricular beat of the previous day had been due to paroxysmal ventricular tachycardia, the focus of origin being ectopic, below rather than in the node.

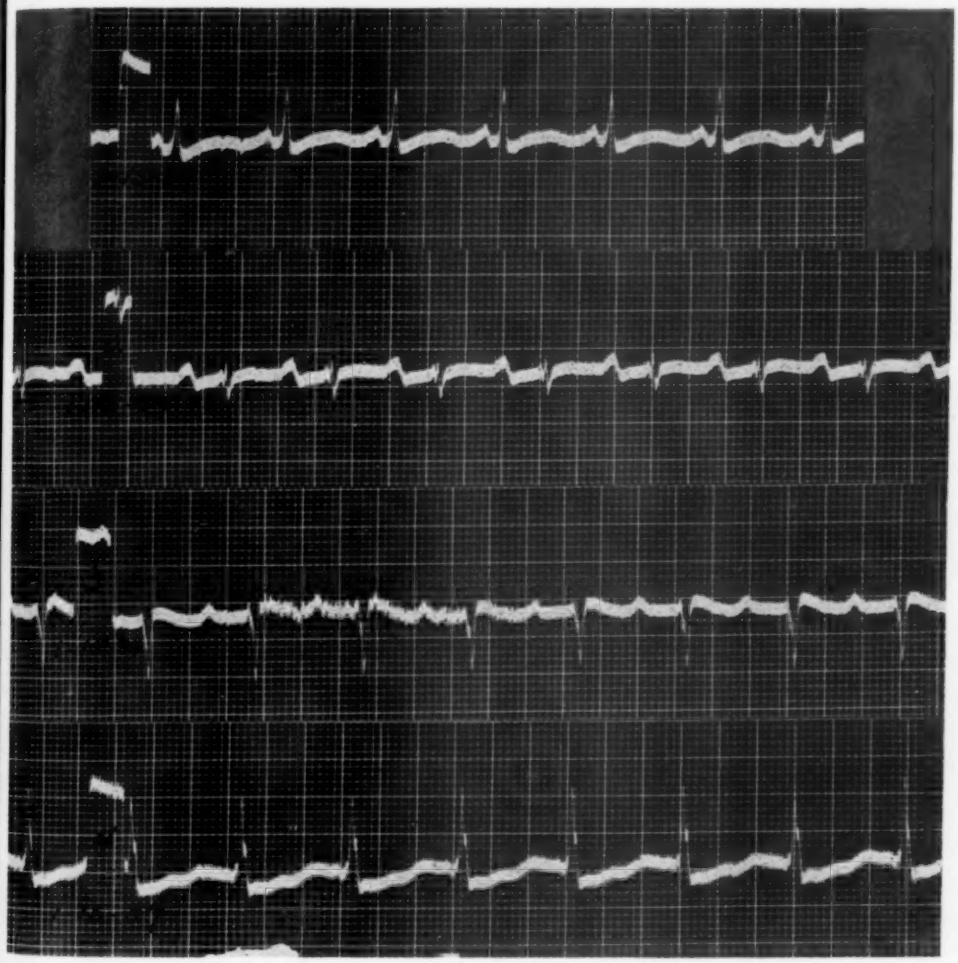

FIG. 3.

On January 15, the electrocardiogram (figure 3) showed a ventricular rate of 105. Left axis deviation was present, T_1 was slightly upright, $T_{2,3,4}$ were not definitely discernible. In Lead I, the P-wave was quite close (about 0.08–0.09 sec.) to the ventricular complex, and the relationship was 1:1. This P was not inverted, and hence not retrograde. In Leads II and III the P–R interval was markedly prolonged, being about 0.24 sec. in Lead II, and about 0.26 sec. in Lead III. Possibly no block was present during the taking of Lead I, but more likely the conduction was so

delayed that each P induced not the ventricular beat immediately following but the next one. It was also possible that complete block still existed with auricular and ventricular rates very nearly the same, but the relationship altered between taking the leads as it might be made to by a ventricular premature beat.

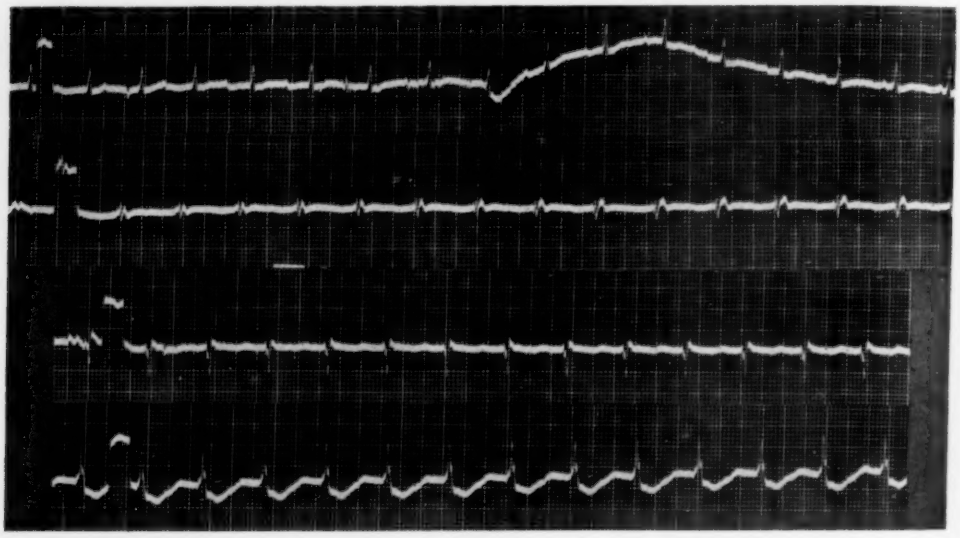

FIG. 4.

On January 16 the electrocardiogram (figure 4) showed complete heart block. The ventricular and auricular rates were so nearly the same that it required many beats before the relative positions of P and QRS were definitely altered. This was probably the status on the fifteenth.

January 17. Heart rate 90.

January 21. Died. Autopsy not secured.

Among the diagnoses were: Paroxysmal ventricular tachycardia; paroxysmal auricular flutter; complete heart block; coronary sclerosis and occlusion.

Case 2. A. P., male, aged 8, was seen in consultation with Dr. W. R. Graves, December 19, 1936. He had been seen on December 14 by Dr. Graves. At that time he complained of abdominal pain and rapid heart beat. He was uncertain which came first. The pain disappeared in a few hours. His past history was negative except for scarlet fever one year ago.

Tachycardia was found, the heart rate varying in rate from 160 to 180 with slight irregularity present. An electrocardiogram taken at the Baptist Memorial Hospital revealed a tachycardia of ventricular origin. On December 19, the rate was still rapid; the apex beat was about 3 cm. beyond the midclavicular line. A soft systolic murmur was present. The liver was slightly enlarged. No edema was present. After a test dose of quinidine sulphate of gr. iii (0.2 gm.) he was given four doses of 4 grains each at two hour intervals. The apex rate dropped to about 120. My electrocardiogram (figure 5) was taken at this point. Mecholyl (0.010 gm.) subcutaneously caused vomiting, but was without result on the tachycardia. A few days later the paroxysm ceased spontaneously.

On January 15, 1937, the heart was only slightly rapid. There was a short squirty systolic murmur at the apex which was at the anterior axillary line. No râles were present, and no edema. Under the fluoroscope, the heart was seen to be

very large, with rounded borders, the left being close to the lateral border of the thorax. The electrocardiogram on this day showed left axis deviation.

About March 17, a paroxysm of tachycardia started accompanied by vomiting. Vomiting and the rapid pulse continued in spite of mecholyl, quinidine and glucose, and on March 19 he died. Autopsy was not secured.

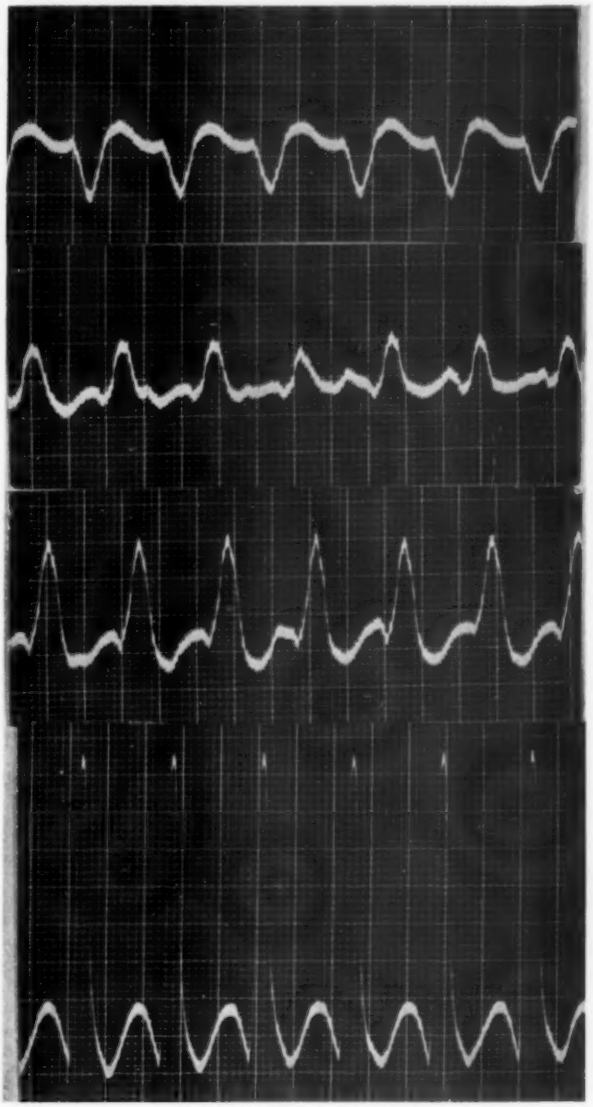

FIG. 5.

Case 3. O. H., Jr., was first seen in 1932 at the age of seven. Two months before he had had influenza, followed by some exhaustion. Three weeks before he suffered an attack of tachycardia (rate over 200, rhythm regular) which lasted for two and a half days. He was given quinidine sulphate, and the attack stopped in a

few minutes (coincidence?). Two weeks later he had another attack which lasted 48 hours. It was not affected by quinidine. The rhythm was regular during the attack but irregular at the offset. The attacks seemed to be associated with mild digestive upsets, nausea and constipation. He had a skin eruption on the flexor surfaces of his forearms which came and went, and which the dermatologist, Dr. E. R. Hall, thought to be allergic.

When seen by me there was no circulatory disturbance, and his physical examination was entirely normal. Fluoroscopy showed no abnormality. Electrocardiography (January 4, 1932) gave an entirely normal tracing except high T_1 (4.5 mm.) and T_2 (5.0 mm.).

He was seen again November 9, 1933. He had had three attacks of paroxysmal tachycardia in the previous three or four weeks, each lasting some length of time. Physical examination showed a heart rate of 112, a questionable systolic murmur at the apex which seemed to be just beyond the nipple.

On November 29, 1935, he was seen again. In the interval he had been examined by Dr. Hugh McCulloch in St. Louis, who it was reported thought the heart was slightly enlarged. On physical examination I found the apex to be 7 cm. to the left of the midline in fifth intercostal space, palpable just beyond the nipple. The right border was 1.5 cm. to the right. There was marked respiratory sinus arrhythmia. The sounds were normal. The rate was 72, the blood pressure 100 systolic and 60 diastolic.

The six-foot teleroentgenogram showed these measurements: RM 3.7 cm., LM 6.6 cm., T 10 3 cm., internal thoracic 19.5 cm., L 11.0 cm.

The electrocardiogram showed sinus arrhythmia; S_1 deeper (5 mm. instead of 2.5 mm.), and altered T-waves. T_1 was upright (5 mm.), T_2 upright (5 mm.) with slightly elevated RT_1 and $_2$ takeoff, T_3 inverted (1 mm.) T_4 upright, and variable (from 2 to 4 mm.). R_3 upstroke slightly slurred. Lead IV was taken from the left chest, fourth and fifth interspaces at left border of the sternum to the left leg.

During the following year, an attack was stopped in six minutes by mecholyl 0.010 gm.

On November 18, 1936, he had an attack of tachycardia which lasted through the next day. Prior to this, he had had a cold with slight fever. During the year he had taken quinidine sulphate prophylactically, but recently had not taken any for several days. With the attack he had pain in the heart area like a hammer, "worse than an earache." He had had pain five times with attacks. The pain was not radiating. On November 21, another attack of tachycardia occurred, and pain began at once, subsiding later, leaving a bruised feeling.

On examination, the apex rate was counted as 176, and was sufficiently irregular to give the impression of auricular fibrillation. The blood pressure was 80 systolic and 60 diastolic. The first sound at the apex had a soft squirting quality.

An electrocardiogram was taken (figure 6) which showed a tachycardia of ventricular origin.

Mecholyl 0.010 gm. was given without result. The attack ceased the next morning.

On January 29, 1937, another attack appeared following a slight sore throat with fever (100° F.) the previous day. Quinidine sulphate gr. i had been taken the previous evening and the morning of the attack. The attack ceased spontaneously just before he was seen, but an electrocardiogram was taken which showed a high T_1 (5.5 mm.) with RT_1 takeoff about 1 mm. high; a high T_2 (9 mm.), cone shaped, with high RT_2 takeoff (1.5 mm.); a high T_3 (3 mm.) with RT_3 takeoff slightly high (0.5 mm.); a diphasic T_4 (plus 4.5 mm., minus 1.5 mm.).

On June 9, 1937, he was in good health. Pulse 76 and blood pressure 105 systolic and 60 diastolic. The pulse showed slight sinus arrhythmia. The sounds were nor-

mal. The heart shadow on fluoroscopy suggested slightly the sabot shape. The teleroentgenogram measured: RM 3.5 cm.; LM 6.7 cm.; T 10.2 cm ; L 13.3 cm.; internal thoracic 23.4. The electrocardiogram showed T_1 upright (5 mm.) with RT_1

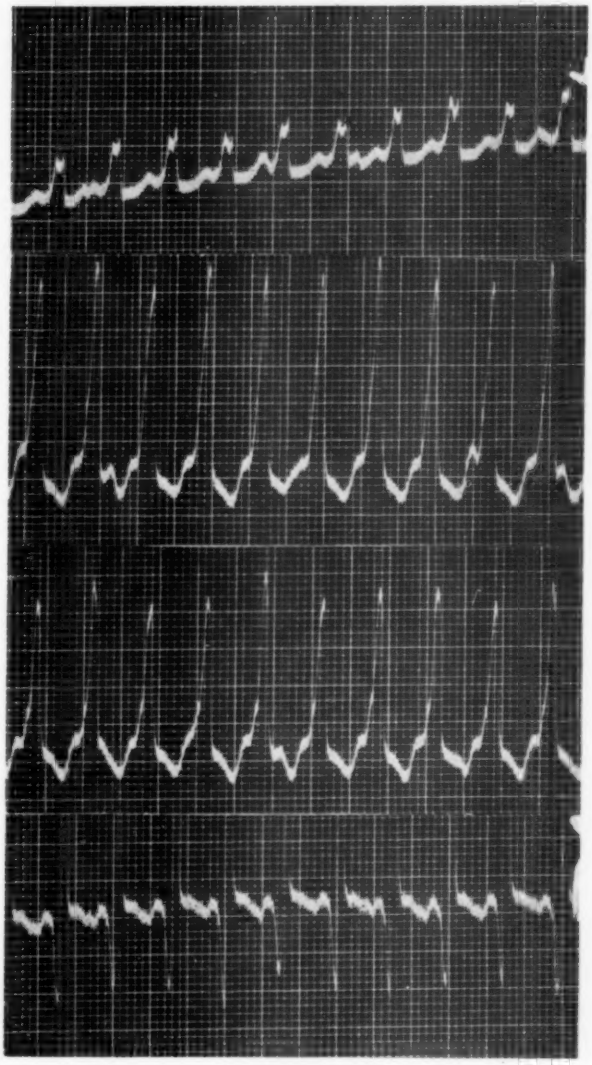

FIG. 6.

takeoff only slightly elevated; a high T_2 (3.5–4 mm.) with high RT_2 takeoff (1 mm.); T_3 was inverted (0.5 mm.) with RT_3 takeoff practically isoelectric; T_4 variable and diphasic (plus 1–2 mm., minus 1 mm.).

The changes in this electrocardiogram, the abnormal T-waves and RT takeoffs, suggest that there is definite myocardial disease present in this boy.

Summary

1. Three cases are presented each showing a paroxysm of ventricular tachycardia. Each heart yielded evidence of organic heart disease, though such evidence is electrocardiographic only in Case 3.

2. Mecholyl was used in Cases 2 and 3, but was unsuccessful in terminating attacks that were proved to be of ventricular origin.

3. One case presented the paroxysm of ventricular tachycardia during an attack of paroxysmal auricular flutter, and later showed a complete heart block during the flutter, and with normal auricular rhythm.

AN ARTICLE CONTRIBUTED TO AN ANNIVERSARY VOLUME IN HONOR OF DOCTOR JOSEPH HERSEY PRATT

OTTMAR ROSENBACH, PIONEER IN THE DEVELOPMENT OF THE CONCEPT OF FUNCTIONAL DISEASE AND FUNCTIONAL DIAGNOSIS IN INTERNAL MEDICINE *

By HYMAN MORRISON, M.D., *Boston, Massachusetts*

OTTMAR ROSENBACH holds a place among the notables in medicine by virtue of the part he played in the development of the concept of functional disease and functional diagnosis. This idea of recognizing and treating disease before structural pathology had actually taken place marks an epoch-making advance in internal medicine, historically in line with its several evolutionary stages.

First, there was the descriptive period dominated by Sydenham (1624–1689). A keen, painstaking observer, Sydenham re-introduced the old Hippocratic method of studying disease at the bedside and during epidemics, and grouped symptoms into clear-cut disease pictures previously undifferentiated or unrecognized.

The next stage began with Morgagni (1682–1771), founder of pathology, and reached its height during the first half of the 19th century in the clinico-pathological schools in France and England with the towering figure of Laennec. New methods of physical examination were invented, notably percussion and auscultation; many diseases were newly described; but more important was the correlation of clinical observation with pathological lesions demonstrated post-mortem.

In the middle of the same century a third step forward was made when physiological and chemical methods became an integral part of clinical investigation. Magendie in France defined medicine as "nothing but the physiology of the sick man," and similarly Virchow in Germany taught that "disease is nothing but life under altered conditions." It became insufficient to men like Traube merely to describe disease; nor would the lesions found in organs after death explain all the symptoms before death. Only by combining experimentation with observation and pathology could internal medicine attain the status of an exact science.

Then came the bacteriological era with Pasteur and Roux and Koch and Ehrlich and Behring. A new technic was developed, and stress was laid on etiology and specific therapy.

All along, many new clinical entities were studied and classified. As they became more familiar, they came to be recognized not only in their typical or classical form, but also in their atypical guise, the *formes frûstes*. Furthermore, this trend led medical thought to concern itself with disease

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in its incipiency, when alterations were only functional and not yet structural. In 1867 Kussmaul began to employ the stomach pump in gastric dilatation with stasis. In 1871 Leube studied gastric function with a test meal and demonstrated occasional deficiency of acid in the stomach. Others described gastric hypersecretion—permanent and transitory, and absence of hydrochloric acid in cases of gastric cancer. In the field of heart disease the term "cardiac insufficiency" was introduced about the same time by Von Dusch. These initial investigations were continued by Rosenbach, a

O. Rosenbach.

disciple of Leube, and it was he who first elaborated the concept of functional disease.

The Man—Biographical Data

Ottmar Rosenbach (b. 1851, d. 1907) was a native of Silesia, of Jewish parentage, the son of a physician, the nephew of Ludwig Traube and also related to Weigert, Ehrlich and Albert Fraenkel. After completing his medical studies at Breslau and Berlin (interrupted for a time by service in the Franco-Prussian War) he became assistant in the medical clinic at Jena in 1873 under Leube and Nothnagel where he remained for four years.

Among other studies, his experimental and clinical researches on the motor function of the digestive and circulatory apparatus, already initiated by his chief, were instrumental in inaugurating a new movement in internal medicine. He continued and elaborated this work in Breslau where he went in 1877; there he came under the influence of Julius Cohnheim. In 1887 he became medical director in the Allerheiligen Hospital, and in the following year extraordinary professor in the University. By this time he had attained eminence both as investigator and clinician, but in 1893 he resigned from the hospital and in 1896 from the University because of differences of opinion. He then moved to Berlin, where he remained to the end of his life, in 1907, devoting himself entirely, except for some consultation practice, to the writing up of previously completed scientific problems—" like an explorer, reaching home, putting in order, and classifying leisurely, the rich treasures he had collected during his travels."

His Work and Motif

In 1909, two years after his death, a selected collection of his writings, in two volumes, was published by Walter Guttmann, friend and former pupil, including a biographical essay and a list of all his works. Even a brief perusal of this list will readily disclose that Rosenbach was a man of unusual energy and versatility, a fearless thinker whose interest reached out over the entire realm of medicine and beyond into the sciences, natural history, and philosophy. In all, 258 publications are enumerated, 14 in book form and the rest monographs and contributions to various periodicals and encyclopedias. Besides, there are mentioned many unpublished manuscripts on various topics—physics, chemistry, psychology, languages, and social medicine. This is the more impressive, when we are told that writing was a great task for him; that he would rewrite each work a number of times before it was published; that many manuscripts remained unpublished because they did not satisfy him; that he would even recall a work already in print for the same reason; that he kept on working to the very end in spite of several years of silent suffering from a malignant abdominal tumor and heart disease; and that all this was done in a relatively short span of life (1851–1907) aside from research, teaching, and hospital and consultation practice. But to work as long as one's strength would allow was the plan of his life, and even on his death bed it was his greatest concern that just those works which he considered most important—one on illusions and the other on certain physical and cosmic problems—were not completed.

I don't write merely for the sake of writing, or to create sensation, or out of desire to fight. I write for the love of science the tools of which are careful observation, extensive experience, logic and sober critique, and the object of which is the recognition and emancipation of the spirit from the yoke of tradition, and not the subjugation of mankind under the shackles of infallible authority. I write for love of the medical profession, whose true representative in my opinion is not the laboratory man, the theoretician or the specialist, but the physician in the fullest

sense of the word, who standing in the midst of life shows fullest sympathy for the patient (armed with the weapons of science but not tied slavishly to authority). I write from the point of view of the physician who recognizes that the suffering of man is an expression of unfavorable energy relationship or psychic influences which can be prevented or cured through no one point of view or method and only seldom through specific curative measures.

I write, finally, out of the deeply rooted conviction that the laity also must not follow authority slavishly, but must be drawn only through study and example to better insight into all health problems. Insight will only then be complete when modern men will have learned again to sympathize with the patient to the highest degree instead of looking upon him as a source of contagion, shut out of human society in blind fear.

This quotation is from the introduction to his book " The Problem of Syphilis "; hence the last allusion. He detested the prevailing hysterical fear of contagion in syphilis, tuberculosis and other infectious diseases, leading to an almost total disregard of the importance of natural predisposition and resistance to infection.

That he should speak in this manner was clearly justified by the wealth of his experience both in the laboratory and in the clinic and by the value of his concepts. Merely citing some representative topics from the list of his publications will give an estimate of the scope of his activity. By far the largest number of his contributions concern themselves with diagnosis; every phase of it to date was covered—physical, clinico-pathologic and pharmacologic, bacteriologic, neurologic and functional. He constantly emphasized, however, that " diagnosis must not be an end in itself or a means for systematic classification—it is the triumph of the art of medicine only when it furnishes a direct basis for prophylaxis and therapy."

In physical diagnosis there are papers on various aspects of auscultation and percussion and paracentesis, on the diagnosis of pleural exudate and on the effect of large pleural effusion on the circulation, on foreign bodies in the bronchi, on Cheyne-Stokes breathing, on cyanosis, on edema, on the diagnostic significance of reflexes, on pulsation of the liver and of the abdominal aorta, on carcinoma of the stomach, on Heberden's nodes, on intermittent hydrarthrosis of the knees, on the coincidence of tabes dorsalis and aortic insufficiency; on fever and antipyretics and thermometry, on chlorosis and other anemias, on diabetes and on the uric acid diathesis, on syphilis, on seasickness, and on epileptic and uremic convulsions. In 1893 there appeared his classic on " Diseases of the Heart and Their Treatment," and in 1903 a translation of his splendid monograph on " Diseases of the Pleura " in the American edition of Nothnagel's System of Medicine.

Another group of papers is on clinico-pathologic and pharmacologic topics: studies on pigment formation in gastrointestinal and metabolic disturbances, on the significance of indicanuria, on tests for bile and glucose, on paroxysmal hemoglobinuria, and on albuminuria; on the antagonism between iodine and the salicylates, on sulphonal and amylhydrate, on the use and misuse of sodium bicarbonate, on chloral hydrate as a sedative in certain

types of dyspepsia, on the effect of digitalis on tissue and visceral tonus, and on morphia.

To neurology he contributed experimental studies in neuritis and on the physiology of the vagus; papers on hemiplegia, on paralysis of the recurrent laryngeal nerve, on the behavior of reflexes in sleep, on the mechanism of sleep, on cardiac neurosis, and on psychotherapy. Particularly noteworthy in this field was his work on the recurrent laryngeal nerves done in his earlier years at Breslau, when interestingly enough his first teaching experience was in the otolaryngological department because that happened at the time to be the only available position. It is noteworthy, also, because his intuitive power is here displayed to a high degree. On the basis of a single case carefully studied and on the critical analysis of similar cases reported in the literature he evolved in 1880 the now well known law "that in compression of the recurrent laryngeal nerve, first the dilators of the glottis suffer and only later are the constrictors involved sympathetically." With further clinical experience he amplified it to the effect that "frequently in affections of the nerve trunks or the central organs the flexors become paralyzed much later than the extensors." This work was recognized seriously only after Felix Semon confirmed it by independent investigation of a large number of cases.

His Attitude to Bacteriology and to Experimentation in Medicine

Although an aggressive opponent to the domination of medicine by the bacteriologic laboratory he recognized fully the biologic importance of bacteriology. "The value of bacteriology as a science cannot be over-emphasized," he said, "and it is capable of inestimable development." His very first publication in 1875 (after his inaugural dissertation in 1873 on a case of calculous pyelitis with perforation into the ascending colon) was on a new kind of grass green sputum, the color of which he demonstrated by cultural methods to be due to spores. Other papers were on malaria and cholera; and his controversy with Robert Koch on tuberculin involved a number of publications on tuberculosis and the tubercle bacillus. In a very stimulating book, "Arzt contra Bacteriologe," available in English translation, he sums up his attitude toward bacteriology and toward experimentation in medicine and also his general philosophy of medicine.

It took no small measure of courage to stand up practically single-handed against Koch, the latter then at the pinnacle of his career, to combat tuberculin as a therapeutic measure; or to disprove the statistics employed in claiming the efficacy of diphtheria antitoxin. But, though a most kind and generous man in personal relationship, he would never compromise in what he considered the truth. "No one will probably refuse to acknowledge that, uninfluenced by the fascinating opinion of the day, I have endeavored to discuss difficult problems from actual experience and in as many different lights as possible, with incisive criticism, but objectively withal. The future will

decide whether I am right or wrong, and in what respect I have gone too far. Children who are now at play will in the end be our judges." Time did prove him correct in his controversy with Koch.

Just because he had experimented much, he warned against over-estimation of experimental conclusions, especially the drawing of conclusions concerning man from results on animals. "Injection diseases and infection diseases," he insisted "are two entirely different phenomena" and he early expressed his conviction that one must consider the clinic and observation at the bedside as predominant in the realm of human pathology. What reason can there be to assume identity of processes, when one taking place clinically shows in every case the effect of individuality and predisposition, whereas the case called forth by experiment does not at all manifest these factors? In disease caused by injection (experiment) there is scarcely any consideration of defensive and compensatory measures; whereas in human infection these factors appearing gradually produce a series of functional and structural changes. Only in a few infectious diseases, such as anthrax, acute miliary tuberculosis, and tetanus, is there an approach to identity between the disease process in man and in experimental animals. Even in these instances, in the case of the disease in man there are the phases of invasion, incubation, and gradual systemic involvement whereas in the experimental animal the organism is suddenly overwhelmed avoiding all defensive agencies, so that invasion and the height of the disease are almost synchronous. If it is considered, further, that comparatively enormous quantities of microbes are utilized for the injections, the differences between disease as observed clinically and disease called forth by experiment will be better appreciated.

I am fully aware that my criticism will be called a retrogression, but I am convinced that it is well-founded. I do not demand that exclusively one domain and one method of investigation should be cultivated, but I merely give it as my opinion that the clinic and the observation at the bedside should be considered the only scales by which results obtained through other methods of investigation must be measured. All laboratory methods, by whatever name they may be called, are only makeshifts, because they imitate disease artificially; they can touch only the extraneous aspect of matters. They may show some objects from a different view-point but they will never present the vital point; the origin and development of the functional disturbance, the ingenious compensation as manifested by the struggling organism under peculiar conditions. They can never be identical with the real mechanism and with the nature of regulative processes encountered as symptoms at the bedside. Experiment, correctly undertaken, enriches scientific knowledge; but it must not pretend to be the guide of practical action at the bedside, for it shows only the limits of compensatory capability, not the form of compensation. . . . Much as I acknowledge the value of operative and exploratory proceedings in establishing correct views as to the functional capacity of various organs—I need only mention extirpation of the pancreas —it is well to keep in mind the limits of these methods of observation, and not to be persuaded that in the majority of these cases the test conditions in an experiment, ever so carefully conducted, may in any wise imitate or be a substitute for slowly progressive changes manifested by disturbances of function which are called disease.

Functional Disease and Functional Diagnosis

Rosenbach's work which particularly influenced medicine dates back to his early years. In 1878, when he was only 27, he contributed two papers which, as previously mentioned, inaugurated formally the new trend in internal medicine of thinking of disease in its earliest manifestations when there is still functional disturbance only and before there is structural or organic change. The first paper entitled "The Mechanism of Gastric Insufficiency" was the result of the work he had carried on at Jena under the influence of his former master Leube.

The crux in the diagnosis of gastric function, digestive as well as motor, is not in the determination of the size of the organ, for this furnishes only uncertain and late criteria. When a stomach is so dilated that its size is undoubtedly abnormal, and its digestive function, as indicated by undigested food content, is so definitely impaired as to make the diagnosis simple, the best that can be hoped for is an arrest of the process, but not improvement. If we desire to cure we must set ourselves not to make a diagnosis of an irreparable pathologic condition, but rather to recognize early the origin of the affection, the beginning of the process, the functio laesa of the organ, and because of this we must lay the main emphasis on functional diagnosis. Medicine as far as possible must free itself from the dominance of the viewpoint of pathological anatomy.

Dilatation of the stomach is not a completed state in the anatomical sense, but rather a gradual process, and we can obtain information on the first stages or milder forms not through anatomical measurement of the size of the organ, but rather through testing physiologically its functions. Just as we cannot reach a conclusion on the strength of the heart from its size, but must consider the tension and quality of the pulse so it is impossible without careful investigation of the efficiency of the stomach to draw a conclusion as to its strength merely through measuring its dilatation.

There is no way of knowing exactly when a stomach is larger than normal. The size of this organ can only be of diagnostic value if it changes under observation. It must be clear then that the stomach will undergo dilatation only when there is a discrepancy between its expelling motor force and an undue resistance. Muscular hypertrophy will compensate for a while the entailed increased work. But as soon as the obstruction is too great or too prolonged, no longer controllable by increased work, there must occur a stretching of the stomach wall through ingested material, and the stretched and overburdened muscle fibers get into a more or less paretic state. But this weakness occurs not alone through mechanical stretching but often through coincident nutritional disturbance of the muscles. Incidentally I want to note that such functional disturbance of the gastric musculature of even high degree will only seldom show microscopic changes—the same is true in the case of heart weakness.

Disproportion between expelling motor capacity of the stomach and increased effort-demands leading to its enlargement may be due either to obstruction or to catarrh, or to unusual amount or quality of food hurriedly ingested; in addition there may be the congenital weakness of the stomach wall or that acquired during acute infections, and upon the degree of paresis of the stomach will depend the extent of the disability; also it is evident that the instances of stomach dilatation hitherto recognized represent but a late end-result of a series of transitory dilatations. A sharp distinction must be made between functional or relative and permanent or absolute dilatation. A large stomach may be normal while a much smaller one may already

clearly show functional disturbance under certain strain. In other words, dilatation of the stomach depends on the efficiency of the musculature and the extent of excessive resistance. With increase of one or diminution of the other there will intervene an insufficiency of the expelling motor forces, resulting in a relative insufficiency of the stomach. Overstepping the functional limits of the stomach, capable to cope with the ordinary tasks, will result in a relative insufficiency which sooner or later will invariably become absolute. So the center of gravity of diagnosis is not in the size of the stomach but in the functional test of its expelling motor force. It seems better thus to choose the name gastric insufficiency for disease phenomena and to reserve the term dilatation for irreparable, end-results of gastric insufficiency.

What are the methods of making a diagnosis of gastric insufficiency? First there is inquiry into the patient's symptoms due to food and eating habits, also the study of vomitus, if present. Then there is the study of gastric contents by means of the stomach tube according to Leube before and after test meals, or at times after indigestible food such as dried berries has been eaten. Sometimes succussion sounds two or three hours after a test meal may be studied, or the rise and fall of the level of the stomach contents as reflected through a speculum, or through sounds produced in the stomach, through compression with inflatable baloons introduced through the stomach tube; or the contractability of the stomach may be tested by filling and emptying the stomach with water. Through these investigations disturbances of the digestive and motor capacity of the stomach can be determined and measures instituted for their correction through appropriate diet in divided quantities.

So the therapy of gastric insufficiency will depend directly on an early exact diagnosis. And, furthermore, by developing this mode of investigation we may succeed in approximating the diagnosis of diseases of the stomach to that of the chest. To attain this objective we must not, however, shun new methods even though it may at first seem as unnecessary as did percussion and auscultation to our predecessors, for we may hope for more happy therapeutic success in diseases of the abdomen because of easier accessibility than in the case of diseases of the chest.

The other paper which appeared in 1878 was entitled "On Experimental Cardiac Valvular Deformities." It was produced under the stimulus of Julius Cohnheim and read as his habilitation thesis when he became privatdozent at Breslau. Working with rabbits and dogs he produced artificially lesions of the heart valves, and found that severe insufficiency and stenosis of the valves could not change the arterial blood pressure, that compensation intervened at once. He attributed this capacity to "the latent reserve force of the heart muscle," a term original with him. "It is, therefore, experimentally established that there is a compensatory mechanism in the heart which can straighten out sudden disturbances in the balance of the circulation." In the same work he attempted also to show when and under what conditions endocarditis may be produced, and to answer what bearing these experiments had on questions of clinical interest.

This concept of insufficiency of organs and a compensatory mechanism through latent reserve force became the "leit-motif" throughout his unusually rich career, and in succeeding years he also described insufficiency of the intestinal tract, and applied this same concept to the kidneys, the nervous system and to disturbance of metabolism such as diabetes and obesity. The physician must not wait until permanent dilatation of the stomach or

heart has occurred or paralysis of the intestines. His aim must be to recognize insufficiency, or the state of disproportion between the demand on an organ and its ability to perform the work. Functional diagnosis must be developed as contrasted with the anatomical form, so that disease may be recognized in its incipiency, in the transition from fatigue to actual change in the tissues and organs. A cure may be achieved then by lessening the load on the organ—impossible after permanent changes have set in.

> Diagnosis should not be an end in itself nor a means of systematic classification but should at all times aim for a balance of energy; it is the triumph of medical art only when it furnishes a direct basis for prophylaxis and therapy. Medical efficiency is not based on the diagnosis of mitral insufficiency or fatty heart, but on the decision as to what is the cause of the disturbance, on the extent of functional disturbance of valve or muscle, on how strong the compensatory forces are, and under what conditions an early disturbance of balance can be restored.

Diagnosis, then, was to Rosenbach but an instrument for better understanding of life in general, so as to enable the physician to see the human individual as a harmoniously well balanced dynamic organism.

> The physician of the future will be compelled to consider, above all, prophylaxis, the rational distribution of the products of internal and external activity—i.e., the correct alternation of rest and labor, the appropriate adaptation to changes of the external conditions of life, and the harmonious development of all physical and mental functions. He will not, in the frame of a formal diagnostic systematism, as a cellular pathologist grasp after symptoms pathognomonic of local changes of tissue, but he will endeavor, as a biologist, to obtain a broad view of the realm of energetics (the province of which is modern organic physiology) and of the total balance of phrenosomatic activity.

His Place in the History of Medicine

Even the fragmentary bits of his life and work recorded here stamp Ottmar Rosenbach as an extraordinary figure in medicine. Yet how little was he appreciated in life, and how few know him now! Partly, this was due to his nonconformist personality. Celibate, retiring yet unusually generous and understanding and genial in a small circle of friends, finding solace with his heroes Heine, Schiller and Goethe, Schopenhauer, Kant and Spinoza, he was almost eccentric in his devotion to medicine. But he was a keen, prodigious investigator, a great clinician, and a fearless, original thinker. He was not always right; in his great zeal to prevent and cure disease by recognizing it in its incipient stages, he often failed to recognize the importance of etiology in disease. Nevertheless his original concepts, worded originally, have become thoroughly integrated in our clinical thought and speech. Especially profound and stimulating in its influence on the development of internal medicine was his concept of functional disease and functional diagnosis. For this he holds a notable place in the history of medicine.

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CASE REPORTS

GENERALIZED ACTINOMYCOSIS; REPORT OF A CASE *

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Since Israel's [1] original paper in 1878 on actinomycosis in man, the disease has been observed with increasing frequency so that it can no longer be considered the rarity it once was. Even as far back as 1899, Ruhräh [2] collected 58 cases that were reported in America, and, reviewing the literature, he found a total of 1094 cases. Of these 56 per cent were of the cervico-facial type, 20 per cent gastrointestinal, 15 per cent pulmonary, 2 per cent skin, and 6 per cent were doubtful.

Numerous reports have followed these early contributions, but few indeed have been the cases of generalized actinomycosis. In 1925 Sanford and Voelker [3] reviewed 670 cases of actinomycosis that had been observed up to that time in the United States. Of these, in only 13 was there a generalized involvement. In 1925 Werthemann [4] collected four cases of actinomycosis with generalization and added two of his own. A number of other reports have appeared in the literature, notably those of Becker,[5] Schinz and Blangey,[6] Shapiro,[7] Kasper and Pinner,[8] Freed and Light,[9] Fellinger and Salzer,[10] and others.

Despite the fact that the generalized form has been reported in the literature in a number of instances, this type of actinomycosis is still rare enough and of sufficient interest to warrant the addition of another case, particularly so since the diagnosis was made ante-mortem.

Case Report

Clinical History: J. C., a white male laborer, aged 47, was admitted to Sea View Hospital June 27, 1936. In February 1936, the patient had developed cough, expectoration, and fever. The cough, moderately severe in character, persisted for several weeks. It then abated somewhat, but a slight cough continued. In April a tender red swelling appeared on the lateral surface of the right lower leg. This was incised, but failed to heal, and continued to drain a thick greenish-yellow pus. In the latter part of April, the cough and expectoration became much worse and on one or two occasions he expectorated a little blood. In May an abscess appeared on the left arm and a week later another abscess developed over the right buttock. In the latter part of May 1936, the patient developed constant dull pain in the right lumbar region associated with chills, sweats, frequency, urgency, nocturia, burning on urination, and a temperature ranging between 102 and 104°. On June 16, 1936 he was admitted to a City General Hospital. There, the abscesses over the buttock and left arm were incised, but continued to drain. Because of the pulmonary symptoms, and because of a chest plate showing a density at the right apex, a diagnosis of pulmonary tuber-

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culosis and possible right pyelonephritis was made and the patient was transferred to Sea View.

Physical Examination: On admission to Sea View Hospital, physical examination revealed a poorly nourished adult male who appeared acutely ill. The teeth were carious. There were impaired resonance and diminished breath sounds at the apex of the right lung. The blood pressure was 114 systolic and 70 diastolic. The heart and abdomen were negative. There was an ulcer on the left arm about one inch in diameter from which a small amount of greenish-yellow pus exuded. The skin margins of the ulcer showed a reddish-purple discoloration, and the surrounding tissue was indurated. A similar ulcer, about two inches in diameter, was seen over the right buttock, and a third was noted on the right lower leg. There was an exquisitely tender swelling in the right lumbar region and the Murphy sign was positive.

Laboratory Findings: The sputum was persistently negative for tubercle bacilli. The urine was clear; specific gravity 1.018; albumin one plus. It showed, microscopically, many clumps of white cells, a few red blood cells, and occasional granular casts. The blood hemoglobin was 51 per cent. There were 2,820,000 red blood cells and 16,800 white blood cells. The differential smear showed 88 per cent polymorphonuclear leukocytes, 6 per cent lymphocytes, and 6 per cent monocytes. The blood chemistry was normal. Blood cultures were negative. The sedimentation rate was 115 mm. in 45 minutes. The Wassermann test was negative.

Roentgen-Ray: The posterior anterior view of the chest showed an opacity in the region of the right apex. This was interpreted as being due to a thickened pleura. (Figure 1.) Roentgenograms of the bones underlying the cutaneous ulcers showed no evidence of bone involvement. The spine was negative.

Course: The temperature was hectic in character, and ranged between 98 and 102°. The pulse rate was 80 to 100. Frequency, urgency, and right lumbar pain were prominent symptoms. On June 30, he developed severe persistent frontal headache. The next day the patient vomited twice. Neurological examination on July 2, 1936 revealed nuchal rigidity and positive Kernig and Brudzinski signs. The cranial nerves were not involved. The deep reflexes were bilaterally markedly exaggerated, and ankle clonus was present. There was a suggestive Hoffman sign on the left, but the other pathologic reflexes were negative. Bilateral choked discs were seen. The spinal fluid was clear and the pressure was 10 millimeters of mercury. The Pandy was positive. There were 320 cells predominantly lymphocytes. The spinal fluid sugar was 37 mg. and the chlorides were 610 mg. On July 3, the patient was comatose. Neurological examination at this time showed in addition to the previous findings, bilateral positive Babinski signs. A spinal puncture was again done. The fluid was under increased pressure, cloudy, and contained 1900 cells per cubic millimeter of which 95 per cent were polymorphonuclear leukocytes. On the same morning an aspirating needle was inserted into the swelling in the right lumbar region and 20 c.c. of thick greenish-yellow, very foul smelling pus were removed. On more careful examination of the pus numerous small yellow granules were observed. These granules, when crushed under a cover slip and examined microscopically, were found to consist of mycelial threads with clubbed ends. The patient died at 5 p.m. on July 3, 1936.

The clinical diagnosis was: Pyemic form of actinomycosis; multiple actinomycotic brain abscesses and meningitis; actinomycotic perinephritic abscess; multiple actinomycotic abscesses of the skin.

Necropsy: The necropsy was performed 16 hours after death. The body was that of an emaciated adult white male. The subcutaneous ulcers previously described were observed on the upper portion of the left arm on its lateral surface, over the right buttock, and over the external malleolus of the right leg. The underlying bones were not involved.

The right lung was firmly adherent at the apex to the chest wall. The left lung was free. The pleurae over the apex of the right lung were adherent and thickened, measuring 2 cm. in thickness. In the apex of the right upper lobe, the lung tissue for a distance of 1.5 cm. from the pleura was firm, flat, grayish-black in appearance, and non-resilient. Just beneath this area and under the lateral pleura there was an emphysematous bleb measuring 1 cm. in diameter. The lung tissue of the right middle lobe was well aerated for the most part. Situated just above the interlobar fissure

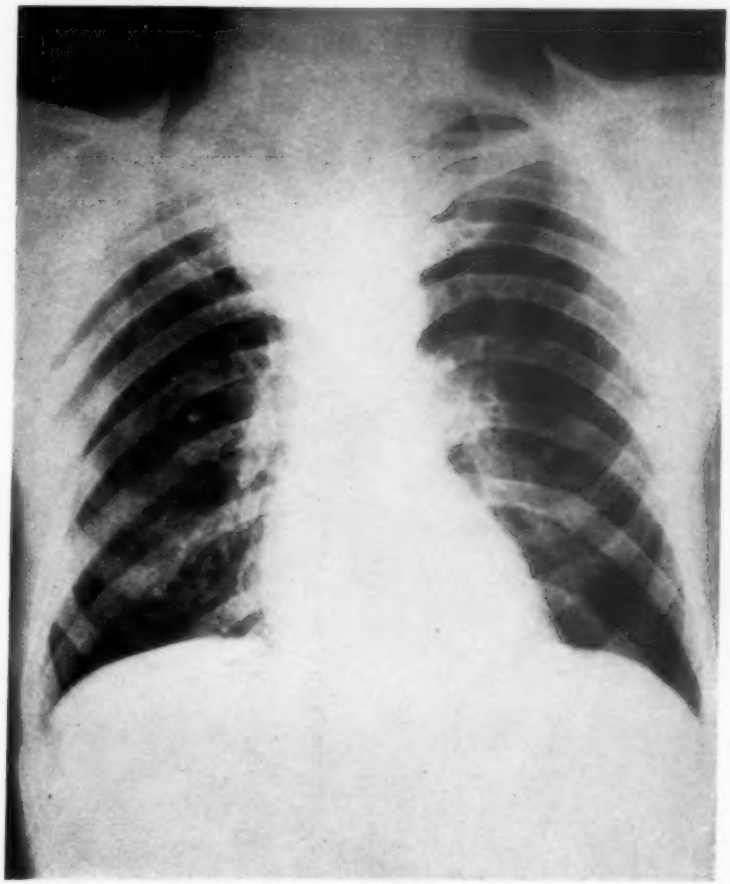

FIG. 1. Roentgenogram of chest showing an opacity at the right apex. At autopsy this opacity was found to be due to a non-specific fibrosis. The primary actinomycotic lesion found at autopsy in the right middle lobe is not visualized.

and 6 cm. from the lateral pleura, there was a soft yellow mass 1 cm. in diameter. This was well encapsulated (figure 2). There was no change in either of the lower lobes. An emphysematous bleb measuring 2 cm. in diameter was seen just beneath the apex of the left upper lobe. The tracheobronchial nodes were enlarged.

Surrounding the right kidney there was a large abscess cavity measuring 10 cm. in diameter. This was filled with thick putrid yellow-green pus. In the posterior portion of the kidney substance near its upper pole, there was an irregular soft yellow mass measuring 6 cm. in its longest diameter. This was composed of necrotic and

purulent material. It communicated with the previously described large abscess and also with the renal pelvis (figure 3). A small amount of pus was present in the right renal pelvis and ureter.

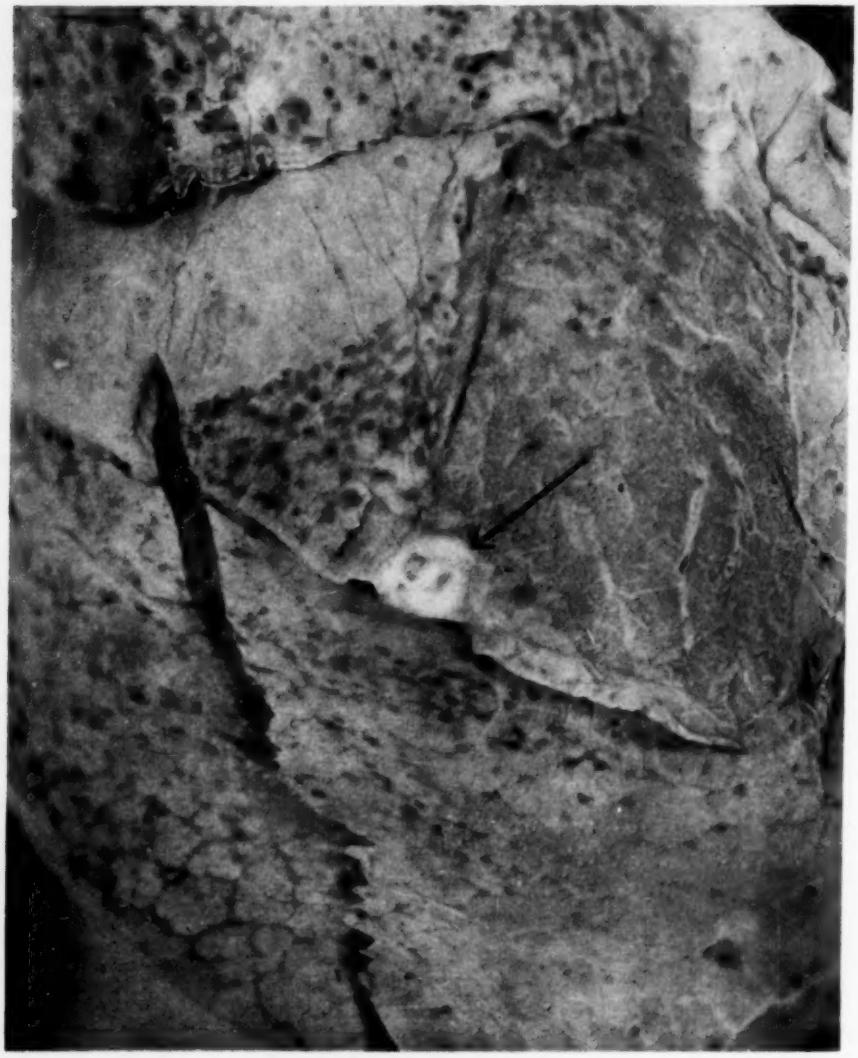

FIG. 2. Gross specimen of right lung showing small primary actinomycotic focus in middle lobe.

On opening the dura, a small amount of thick green pus was seen over the occipital and right frontal regions. The meninges were markedly congested. In the anterior portion of the right frontal lobe two abscess cavities filled with greenish-yellow pus were noted. The larger measured 2 cm. and the smaller 1.5 cm. in diameter. A similar abscess 1 cm. in diameter was found in the right parietal lobe and another in the cortex of the left occipital lobe (figure 4).

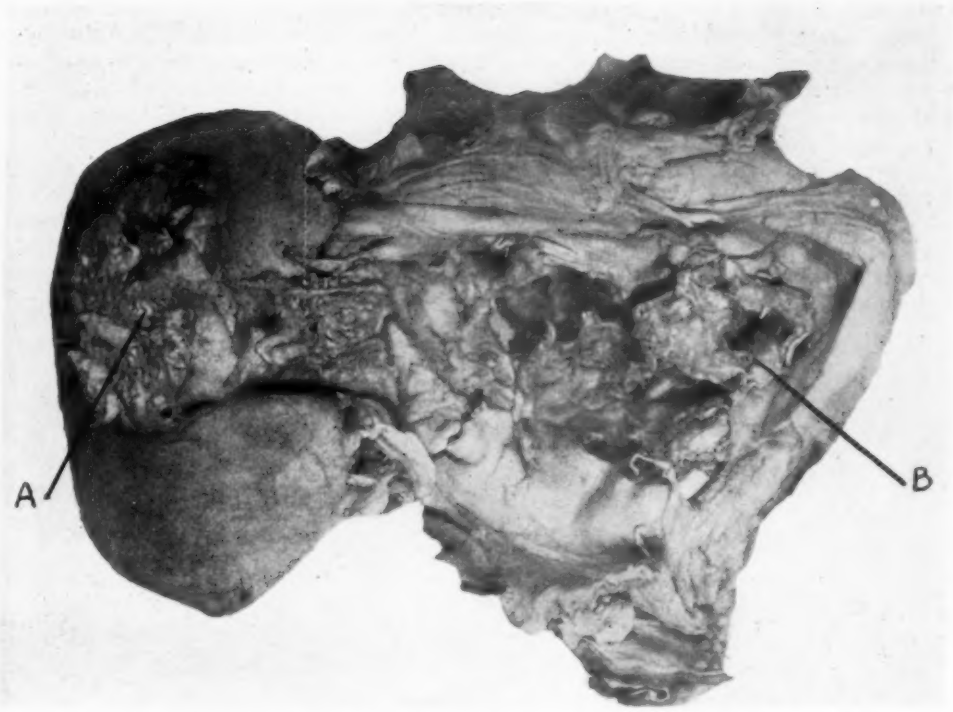

FIG. 3. Actinomycotic abscess (A) in kidney substance and (B) perinephritic abscess.

FIG. 4. Section of brain through occipital lobe showing actinomycotic abscess.

Histopathology:

Lung: In the section of lung through the small yellow mass described grossly, there was an abscess composed of a dense accumulation of polymorphonuclear leukocytes with a few lymphocytes and large mononuclear cells. At the periphery of this abscess a ray fungus was seen. This consisted of a central granular mass with peripheral club formation. In the Gram stain, the central mass was seen to consist of branching mycelial threads. The abscess was surrounded by granulation tissue composed of epithelioid cells, fibroblasts, lymphocytes, and collagen fibers.

Kidney: In the section of kidney there was an abscess composed of polymorphonuclear leukocytes, nuclear remnants, lymphocytes, and large mononuclear cells. Several ray fungi were seen (figure 5). These were similar in character to those described in the lung. The wall surrounding the abscess was larger in diameter than

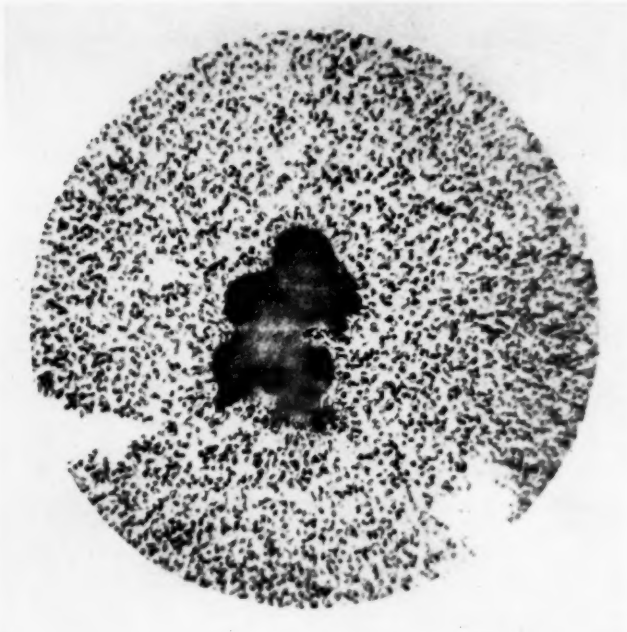

FIG. 5. High power section through kidney abscess showing ray fungus.

that seen in the lung and was composed of lymphocytes, epithelioid cells, and polymorphonuclear leukocytes. Very little fibrous tissue was seen.

Brain Abscess: In this section an abscess was seen which was composed chiefly of polymorphonuclear leukocytes, but also of lymphocytes, and nuclear remnants. Occasional ray fungi were present. The wall of the abscess contained epithelioid cells, lymphocytes, fibroblasts, large mononuclear cells, and a few polymorphonuclear leukocytes. Within the cytoplasm of the large mononuclear cells fat droplets and necrobiotic nuclei were observed. Collagen fibers were present in moderate amount at the periphery of the wall of the abscess. In the leptomeninges the blood vessels were engorged and there was a dense infiltration of lymphocytes, large mononuclear cells, and occasional polymorphonuclear leukocytes.

Skin Ulcer: In the corium as well as in the subcutaneous tissue there was a collection of lymphocytes, mononuclear cells, epithelioid cells, fibroblasts, and a few polymorphonuclear leukocytes. The capillaries were engorged.

Anatomic Diagnosis: Primary actinomycosis of the right middle lobe of the lung; generalized actinomycosis with actinomycotic abscesses in the brain, right kidney, and skin; actinomycotic meningitis; actinomycotic right perinephritic abscess; fibrosis of the apex of the right lung (non-specific); emphysematous blebs in both lungs; dilatation of the heart; diverticulum of the rectum.

Comment

For many years the dispute over the etiology of actinomycosis revolved itself around the question as to whether the organism was the anaerobic one of Wolf-Israel [11] or the aerobic one of Bostroem.[12] Bostroem's organism is exogenous and is found widely distributed on grain and plants. The Wolf-Israel type is anaerobic, grows at a temperature of 37 degrees and will not grow at room temperature. Wright [13] obtained cultures of the anaerobic organism from clinical cases of actinomycosis and concurred with Wolf-Israel in their conclusion that the anaerobic organism was the etiologic agent. In 1910 Lord [14, 15] found organisms with the morphological and staining reaction of actinomyces in carious teeth and in tonsillar crypts of normal individuals. When this material was injected intraperitoneally into guinea pigs, it gave rise to tumors which histologically were similar to actinomycotic tissue. He concluded that the buccal cavity was a normal habitat of actinomyces and was the source of infection. As a result of this work the previously widely accepted conception that chewing infected grain or straw led to actinomycosis was quite generally abandoned, and the aerobic organisms were considered entirely saprophytic.

Naeslund [16] after extensive investigation with various strains of both aerobic and anaerobic organisms has found that there are pathogenic and non-pathogenic strains of each type. He thus divides the pathogenic actinomyces into two groups, actinomyces-alpha and actinomyces-beta, and gives the following characteristics for each:

Actinomyces-alpha: Found in the mouth and gastrointestinal tract of normal individuals and not found free in nature. It is chiefly anaerobic, grows best at body temperature, and little or not at all at room temperature. It is rarely acid fast, never forms spores, and shows little resistance to drying. It forms long threads and clubs in the body and usually shorter rods on artificial media. Growth on agar is very slight. It is quite pathogenic for cattle but only slightly so for guinea pigs and rabbits. Its portal of entry in the human body is the mucous membrane of the mouth and intestines, and less often the lungs. It usually produces actinomycosis of the cervico-facial type and of the gastrointestinal type and rarely of the lung. Spread of the disease occurs by direct extension. Generalization through the blood stream is rare. The clinical course is, as a rule, mild. There is little or no fever and the prognosis with treatment is good.

Actinomyces-beta: Found free in nature, is aerobic, and grows well on agar at room temperature. Spore formation is common. It forms long threads in the body and on media, but club formation is not common. It strongly resists drying. It is quite pathogenic for guinea pigs and rabbits and less so for cattle. The portal of entry in the body is usually the lung and less often the skin. The fungus reaches the lung either by means of inhalation or by aspiration from the mouth. It, as a rule, produces actinomycosis of the lungs and

spreads by direct extension and by metastases through the blood stream. The course of the disease is relatively rapid and usually fatal.

The two types, however, can not be too sharply demarcated since cases have been reported in which the organism could be grown both aerobically and anaerobically (Naeslund,[16] Fellinger and Salzer [10]).

In our case, we were unsuccessful in obtaining a pure culture although numerous attempts were made under both aerobic and anaerobic conditions and with several types of media.

The primary lesion in the generalized form of actinomycosis is, in the very large majority of instances, located in the lung. In a review of 20 cases described in the literature and including our own, the primary lesion was in the lung in 15, in the cervico-facial region in two, and in three it was doubtful. Although the lower lobe is usually the seat of the focus, it not uncommonly is seen in the upper lobe.

The size of the primary lesion as observed at autopsy varies greatly. It may be very small, in fact, so small that it can be missed entirely unless carefully searched for. In our case the small focus was not found at autopsy until the second examination of the lungs was made. Even the roentgen-ray plate of the chest, perhaps because of the anatomic location of the nodule, did not reveal evidence of its presence. It is extremely important to keep this fact in mind. Several cases of primary actinomycosis of the brain have been reported (Howard [17]) although it is most difficult to explain how this organ can be the primary seat of the disease. As Jacoby [18] points out, it is quite possible that in these cases, either the true primary lesion was missed by the pathologist, or else the patient had a small primary lesion during life which was not observed by the physician and subsequently healed. The evidence for the conclusion that the pulmonary lesion was the primary one in our case is that, in the first place the pulmonary symptoms were the first to appear, and secondly, the anatomic character of the lesion observed at autopsy indicated that it was the oldest in the body.

The primary lesion can and very frequently does spread by direct extension to involve a large portion or the entire lung. It may extend by continuity to the pleura producing an empyema, into the chest wall with the formation of an abscess, and into the pericardium and myocardium. Progression by way of the lymphatics is denied by most authors. The lymph nodes are usually enlarged and edematous, but rarely show evidence of the actinomycotic process. In a case reported by Werthemann,[4] however, the tracheo-bronchial glands were definitely involved. Generalization by way of the blood stream in instances of primary actinomycosis of the lung does not appear to be very uncommon. The organisms invade branches of the pulmonary veins and thus enter the general circulation. Kasper and Pinner [8] and Fellinger and Salzer [10] both demonstrate beautiful histological sections which show the ray fungi within the pulmonary veins.

Metastases may be wide spread, involving many organs, or they may be very few in number. The brain was the most common location for metastases in the cases reviewed, being affected in 15 of the 20 cases. In the order of decreasing frequency, metastases occurred in the kidneys, the skin and subcutaneous tissue, the spleen, the lungs, the heart, the liver, the bones, the thyroid,

the intestinal wall, the lymph nodes, and the testicle. There were three perinephritic abscesses in the 20 cases. It is interesting to note that metastatic involvement was greater in those instances in which there was involvement of the heart.

When the brain is affected metastatically in generalized actinomycosis, abscess formation is the most frequent type of lesion. There may be one or several abscesses, and there appears to be no predilection for a particular lobe. The meninges can be secondarily involved. Abscess formation was present in 13 of the cases reviewed. In one (Fellinger and Salzer [10]) a subarachnoid granuloma was seen, and in another (Snoke [19]) the meninges alone were involved. This is contrary to the findings noted in actinomycosis of the central nervous system resulting from direct extension of an aural lesion. In these, meningitis is frequent and abscess formation less common (Moersch [20]).

The heart and pericardium may be involved by direct extension or by the hematogenous route. When the blood stream is the avenue of approach, numerous small abscesses are found in the myocardium. One of these may break into a chamber of the heart and thus provide a second source of dissemination. When the spleen, liver, thyroid, intestine, and lungs are affected secondarily, many small abscesses are generally found. In the intestine they are seen within the wall. The kidneys may show multiple small abscesses or there may be a single large abscess in the cortex of one kidney which extends into the pelvis, or peripherally, giving rise to a perinephritic abscess. Bone can be invaded by direct extension from a neighboring organ, but in most instances actinomycosis of the skeletal system is the result of a hematogenous spread. Even the mandible which is so close to the most frequent site of actinomycosis, the cervicofacial region, is rarely invaded by direct extension (Kaufmann [21]). The spine is the most common of the bones affected. There are sharply defined abscesses, as a rule present in two or more vertebrae. The bodies, pedicles, and laminae are attacked, but the intervertebral discs are usually spared. A marked destruction of the vertebral bodies may occur without collapse or kyphosis (Tabb and Tucker [22]).

It is beyond the scope of this paper to discuss at any length the varied and bizarre symptoms that can occur in a pyemic disease of this kind. The symptomatology will, of course, depend upon the organs affected and the extent of disease in these organs. Before generalization has occurred the symptoms are those of the primary lesion. If it be in the lung, as it usually is in these cases, then the severity of the symptoms will usually be proportional to the extent of the lesion. Cough and expectoration of sputum which is occasionally blood streaked are prominent complaints. Pain in the chest, night sweats, fever, and loss of weight are not unusual. The sputum may be thick, copious, and fetid, or it may be scanty and odorless (Christison and Warwick [23]). Once generalization has occurred, the symptoms referable to other organs affected may be so prominent that they completely overshadow those of the primary lesion and one has to question the patient carefully to learn the nature of the onset of the illness.

The temperature is hectic, usually ranging between 98 and 102 degrees. The pulse rate is proportional unless there is cerebral involvement with increased intracranial pressure. Chills and sweats are frequent. The white blood cell count ranged between 10,400 and 19,600 in those cases in which it was reported.

The differential counts showed between 82 and 88 per cent polymorphonuclear leukocytes and 12 to 18 per cent lymphocytes. Moderate secondary anemia is usually present.

Perhaps the most important factor in the diagnosis is to remember that this disease, although extremely rare, does exist. It should be considered in all pyemias whose origin and nature are not apparent. The duration of the entire illness in the cases reviewed ranged between three months and two years. However, it was not always possible to determine from the histories given approximately when generalization had occurred. It is likely that most patients live but a few months after metastases are evident.

A careful search of the sputum should be made when the disease is suspected. If sulfur granules are present and these, on microscopic examination, show the mycelia, the diagnosis is definite. It is not sufficient to culture a routine sputum specimen for fungi. As was mentioned before, actinomyces have been found in the mouths of normal individuals, and a positive culture may readily lead to error.

A careful examination of pus obtained from secondary foci may lead to the diagnosis as it did in our case. This, of course, is not always possible. Biopsy examination is indicated whenever it can be done. Blood cultures have been almost uniformly negative. Fellinger and Salzer [10] obtained a culture from the postmortem blood which was pathogenic for laboratory animals. Freed and Light [9] claim that they obtained four aerobic cultures in their case during life, but no attempt was made to produce the disease in animals.

Attempts have been made to develop an intradermal reaction as a diagnostic test in actinomycosis, but the results thus far have been controversial and discouraging. De Area-Leao [24] reported distinct cutaneous reactions in two cases of actinomycosis when 0.3 c.c. of a filtrate from an old broth culture of actinomyces bovis was injected intradermally. Normal individuals gave no reaction to such injections, and control injections of sterile broth also failed to give positive results. Adant and Spehl [25] also obtained positive intradermal reactions in two cases of pleuro-pulmonary actinomycosis by using a filtrate of an old culture of actinomyces bovis. The reaction appeared 12 hours after injection, was characterized by erythema, an indurated zone 2 to 3 cm. in diameter, and disappeared in four or five days. They also obtained negative results in normal individuals, but did observe positive reactions in patients having other types of mycotic infections. They concluded that a positive reaction was indicative of a mycotic process in the body, but was not specific for actinomycosis. On the other hand, Mathieson, Harrison, Hammond, and Henrici [26] found that normal individuals gave more frequent and more marked skin tests to actinomyces bovis than did actinomycotic patients.

Summary and Conclusions

A case of the generalized form of actinomycosis has been presented. The primary lesion is, in most instances, in the lung. Metastases may be wide spread or few in number. The brain is the most frequent organ secondarily involved. The symptoms are varied depending upon the organs affected.

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ABNORMAL SENSITIVITY TO LIGHT IN A CASE OF POSSIBLE LANDRY'S PARALYSIS *

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THE purpose of this report is to describe a condition of acute hypersensitivity to light occurring in a patient during the earlier stages of a fatal ascending paralysis resembling the type described as Landry's syndrome, and to discuss the relationship of this condition to other types of photosensitivity. The patient remained in the hospital for a period of two weeks, during which time it was possible to make a rough characterization of her sensitivity to light. No definite diagnosis of her condition was made at the time, although certain neurological changes were observed. A few days after returning to her home in a nearby city, acute dementia and marked paralysis—first of the feet, then of the legs, and on up—developed; and she died on February 17, 1935. No autopsy was performed, but the clinical diagnosis made by the attending physician was Landry's paralysis.

When first observed in the hospital, the patient displayed a fiery erythematous dermatitis on the face, hands and arms. The delimitation of this dermatitis was such as to suggest that it was the result of exposure to light; only the face, hands and arms were affected and these only on the parts which would be most exposed to sunlight. The submental triangle, and the interior surfaces of the hands and arms which would ordinarily be shielded from light showed little or none of the erythema. A very striking demarcation existed between the erythematous exterior surfaces of the hands and arms, and the more or less normal medial surfaces; this is shown in the photograph reproduced as figure 1, which was taken after the patient had been in the hospital for two weeks protected from direct sunlight, and the erythema had begun to fade. The dermatitis was more noticeable on the lower arms and the hands than on the upper arms, as though the periods of exposure had been different due to the wearing of different sleeve lengths. No trace of the dermatitis appeared on any portion of the body which might not have been exposed to light under ordinary circumstances. The answers of the patient to questions regarding exposure to sun were not trustworthy; at one time she denied having been recently exposed directly to sunlight, but at other times stated that she had been so exposed. The following is a summary of the history, physical, and laboratory findings other than sensitivity to light.

CASE REPORT

G. K., a 40-year-old white American housewife, was admitted to the University of California Hospital on January 6, 1935.

Chief Complaints: Swelling of the face, with a burning, itching eruption of the face, hands and arms; progressive weakness; and vomiting.

Family History: The maternal grandfather died of cardiac disease, and the maternal grandmother of renal disease. No history of tuberculosis in the family was obtained.

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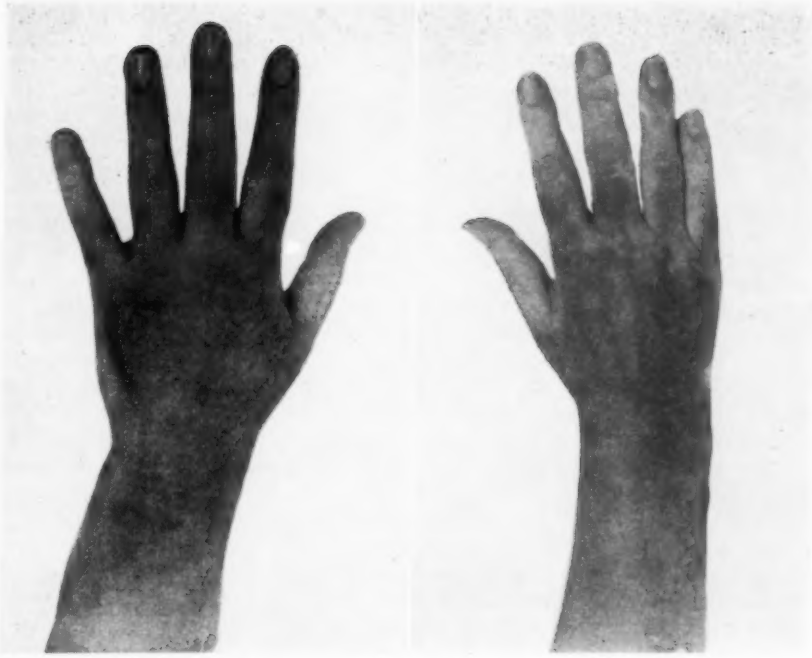

FIG. 1.

Marital History: The patient had been married for 21 years. Her husband was living and well, age 41. Two children, ages 7 and 19 respectively, were living and well. There had been no miscarriages or abortions.

Past History: The patient had pneumonia at the age of 12, and again when she was 39 years old. She had scarlet fever when she was 21 years old; and at the same age, when her first child was born, she was confined to bed for several weeks with fever, pleurisy and hemoptysis. Tonsillectomy and appendectomy were performed at the age of 28. At the age of 30, she was confined to bed for two months because of shortness of breath and tachycardia. Cholecystectomy was performed when she was 28 years old, for cholecystitis and cholelithiasis; recovery was uncomplicated.

Menstrual history was negative except for two periods missed between October and December 1934.

The patient has been obese since the age of 27; average weight, 225 pounds. Her weight reached a maximum of 250 pounds when she was 34 years old. At the time of admission to the hospital she weighed 216 pounds.

Present illness began with a sore throat and fever in October 1934, three months prior to entry. This was followed in two days by generalized muscular tenderness and soreness. The patient went to bed, and remained in bed until she entered the hospital. A week after the onset of illness she was seen by the family physician, and quinine in capsules was prescribed. Several days later, after she had taken 12 of these, an eruption appeared—first on the cheeks, then on the hands, arms and legs, and eventually over the entire body. This eruption consisted of minute red areas, which later coalesced to form purpuric patches. The quinine was discontinued, and sodium salicylate was given by mouth. Her fever gradually subsided. Marked swelling of the face with brawny induration appeared, later extending to the dorsum of the hands and forearms.

After one month the brawny induration and eruption of the skin had disappeared except that of the face, an exposed area of the chest not covered by her nightgown, and the extensor surfaces of the hands and fingers. These areas felt hot to touch, although the patient had no fever at this time. Parts of the skin not exposed to light showed no discoloration. One month after the onset of illness, heavy traces of albumin appeared in the urine, and were present there for one month during which time the patient's legs and forearms were quite noticeably swollen. This edema subsided as the albuminuria disappeared.

Shortly after the onset of her illness, the patient noticed weakness of the extremities, especially of the legs. This weakness progressed until, at the time of entry into the hospital, she was unable to rise from a sitting position.

Six weeks prior to entry, the patient began to have attacks of vomiting, which occurred usually in the mornings after breakfast; later, though not frequently, at other times of the day. Her appetite became poor, but loss in weight was slight. A study of her dietary habits previous to her present illness revealed no outstanding deficiency. During her illness previous to entry, her diet had consisted mainly of citrus fruits with the occasional addition of toast and cereal. For three weeks before entry, all medication was withheld without causing relief of her symptoms; and darkening of the patient's bedroom had no appreciable effect on the skin lesions.

Physical examination showed an obese woman, lying in bed in no apparent distress. The appearance of the skin has been described elsewhere. The heart and lungs were negative. Pulse was regular in force; rhythm 120 per minute. Blood pressure with the patient prone was 150 mm. of mercury systolic; and 95 mm. diastolic. The abdomen was very obese, and covered with numerous striae. An upper right rectus scar was present, and an old appendectomy scar. No abdominal organs or masses could be palpated. Pelvic examination showed an irregular, torn cervix, and the presence of a leukorrheal discharge. Rectal examination was negative. There was muscular weakness in all extremities, and the muscles were flabby. Arm reflexes were present but hypoactive. Knee jerks could not be obtained. Ankle jerks were present. Plantar response was normal. There was reduced sensitivity to pinprick over the medial aspects of both legs from the knee to the ankle, as well as over both deltoid regions and the upper outer chest. The reactions to heat, cold and vibration were normal.

Laboratory Tests:

Urine: Dark brown to brick-red in color; acid; sp. gr. 1.030 to 1.041. Albumin: faintest possible trace, to negative. Reducing bodies absent. Acetone negative. Sediment (uncatheterized specimen) showed 20 pus cells per high dry field; no casts; no red blood cells. Spectroscopic test for hematoporphyrin negative.

Stool: No occult blood; no parasites.

Blood: Hemoglobin (Sahli) 85 per cent (12.3 gm.); red blood cells 4.05 to 4.65 million per cu. mm.; white blood cells 7,200 to 5,550 per cu. mm. Differential count: PMN. 58 to 70 per cent; PME. 0 to 5 per cent; PMB. 0 to 1 per cent; lymphocytes 20 to 21 per cent; and monocytes 20 to 16 per cent. The red blood cells showed slight anisocytosis and poikilocytosis. Platelets appeared normal in number.

Blood Kahn and Kolmer quantitative test: negative. Non-protein nitrogen: 30.8 mg. per cent. Creatinine: 1.3 mg. per cent.

Gastric analysis: Free hydrochloric acid present.

Basal metabolic rate: Plus 24 per cent (probably inaccurate as patient was restless and uncoöperative.)

Tuberculin skin test: Negative to 1 c.c. of 1:1000 human.

Electrocardiogram (interpreted by Dr. Wm. J. Kerr) showed a rate of 103 per minute; regular rhythm; left ventricular preponderance; slurred QRS complexes.

Roentgen-ray examination of the chest (by Dr. R. S. Stone)—films and fluoroscopy: The heart appeared to be enlarged transversely. The lungs appeared clear. The spleen could not be seen under the fluoroscope.

Course: The patient was placed on a diet of 1,200 calories. Sodium amytal and later chloral hydrate were administered for sleeplessness. Massage and passive exercise of all extremities were given. During the first four days there were slight daily elevations in temperature, the highest being to 37.7° C. on the day of entry; throughout the remainder of her stay in the hospital, the patient's temperature was usually normal, occasionally rising to 37.5° C. Her pulse varied between 80 and 120 per minute. Vomiting occurred on only a few occasions, chiefly when she was disturbed by diagnostic procedures.

Throughout her stay in the hospital, no apparent change occurred in the patient's general condition. She remained irritable and uncoöperative, and was somewhat resistant to all examinations. Details of the diagnostic studies made to determine the etiology of the skin lesions are described below. The patient was discharged from the hospital on January 23, 1935.

Subsequent course: The following information was received from her family physician: "About four or five days after returning home, the patient began to complain of increasing weakness in both limbs below the knees, together with recurrent attacks of vomiting. A flaccid paralysis set in, involving first the feet; then the legs, thighs, body muscles, upper extremities; and finally the muscles of deglutition. The patient became delirious; her temperature rose rapidly; and she died on February 17, 1935. No autopsy was obtained.

"At no time did she complain of any pain; there were no convulsive seizures or muscle spasms, nor was there any incontinence, urinary or fecal.

"The diagnosis made by the consulting neurologist was Landry's ascending paralysis."

Experimental

Reproduction of the Lesions by Quartz-Mercury Arc Radiation. On a number of occasions small areas of the skin of the thighs were subjected to the radiation from a quartz-mercury arc in doses which were estimated as capable of producing only a very mild erythema in normal skin. The patient always responded to this treatment with erythema much more severe, and much more persistent than that produced in normal individuals by similar doses; and in the course of a few days the irradiated areas developed the appearance of the erythematous dermatitis which covered her face, arms and hands. We will describe a single controlled experiment: An area of the skin of the thigh, about 5 cm. square, was exposed to the radiation from a quartz-mercury arc of the Hanovia Alpine Sun type, for a period of three minutes at a distance of 20 inches. To serve as a control, a light complexioned, healthy individual was given a like exposure, at the same time. Within a few hours the normal individual developed a very mild erythema of the irradiated area, which faded in the course of the following day and on the second day could be no longer detected. The patient developed an erythema at about the same time as the control, but which, in contrast, increased in intensity for several days. On the second day following the irradiation the patient showed a bright red erythema of the irradiated area, at which time the control exhibited no further traces of reaction to the exposure. Three days later the exposed area was still bright red and showed a slight scaling; it resembled very closely the erythematous dermatitis exhibited by the face and arms. This erythema persisted until the patient

left the hospital 11 days following the irradiation, at which time it was beginning to fade. Another area irradiated two days previous to the above still showed erythema at the end of 13 days, and was beginning to exhibit definite signs of pigmentation at that time.

One area which was given a number of successive irradiations developed a somewhat less severe erythema than the others. The explanation of this is difficult, but it is possible, since this experiment was performed somewhat later than any of the others, that the patient's sensitivity was beginning to decline.

We feel that in these experiments we have reproduced the lesions which this patient displayed on entering the hospital by relatively mild exposure to quartz-mercury arc radiation, her response to such radiation being much more severe and persistent than that of normal individuals.

Delimitation of the Wave Lengths Producing the Erythema. The importance of determining what wave lengths produce abnormal sensitivity to light has been stressed elsewhere by the writer (Blum, 1933; Blum et al., 1935). Such a study provides the possibility of deciding whether the abnormal sensitivity is due to a hyperactivity of the normal photodermal mechanism, or is due to the activity of an abnormal photosensitizing substance as is the case in *urticaria solare* (see Blum, Allington and West, 1935). To determine which part of the mercury arc spectrum was active in producing the erythematous reaction described above, we exposed five areas on the thigh simultaneously to the same dose of quartz-mercury arc radiation used in the experiment described above; one of these areas was exposed directly to the full radiation of the arc, while the other four were covered by glass filters of different spectral transmissions (774, W.G., 385, 038, figure 2). A severe erythema of the type described above developed on the area exposed directly to the arc, but no changes were detected on any of the areas covered by the filters. On a later occasion fresh areas were covered with the filters and exposed to the arc for a period of 15 minutes, but again no changes were observed; an exposure of this duration to the direct arc should produce a severe burn in a normal individual.

The curve N.E. in figure 2 shows the relative effectiveness of various wave lengths in eliciting erythemal response from normal skin, from which it will be seen that no wave lengths greater than 3200 Å are effective. The filter transmissions are also shown in this figure, and it will be seen that any of the filters used above (774, W.G., 385, 038), which prevented the production of the abnormal erythemal response in our patient, will also prevent the production of erythema in normal skin, since all remove the radiation shorter than 3200 Å, except 774 which permits only a very slight fraction of the erythemic radiation to pass. On another occasion an area was irradiated through filter 970 for a period of three minutes, with the result that a milder erythema developed than that produced by the full arc although more severe than that which would be elicited from normal skin by such a dose. Figure 2 shows that this filter permits only a part of the normal erythemic radiation to pass, so that the effectiveness of the dose should be considerably decreased.

These experimental facts lead to the conclusion that the wave lengths which produce the abnormal erythematous response in our patient are the same as those which produce erythema in normal individuals. While we cannot rule out the possibility of an abnormal photosensitizing substance having its ab-

sorption spectrum in the same region as that of the substance responsible for normal erythema, it would seem reasonable to neglect this rather vague hypothesis and assume that the abnormal sensitivity of our patient represents a hyperactivity of some part of the normal photodermal mechanism.

A much more careful analysis of the spectral sensitivity would be required to give complete justification to this last assumption, but such an analysis would require considerable time and equipment and would not be feasible as a rule when such cases come to observation. On the other hand, the equipment used in the above experiments should be available in any hospital. If a set of filters of known spectral transmissions is not at hand a great deal may be learned by

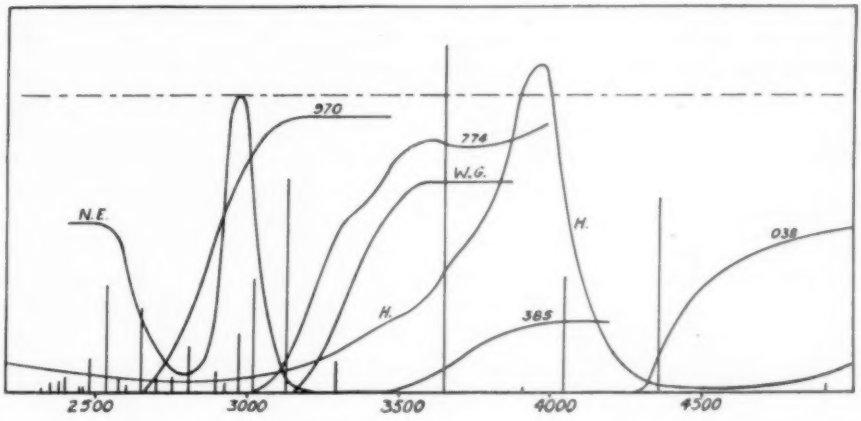

FIG. 2.

Abscissa—wave lengths in Ångstrom units.
Ordinates—arbitrary values.
N.E.—normal erythemic response (after Coblenz and Stair, 1934).
H.—absorption of hematoporphyrin (values of ϵ calculated from Clar and Haurowitz, 1933).
970, 774, 385, 038—transmissions of Corning glass filters characterized by these numbers.
W. G.—transmission of a window glass filter. The broken line represents 100 per cent transmission of the filters. The transmission of filter 038 was determined by means of a spectrophotometer; the transmission of the other filters was determined by means of a quartz spectrograph.
Vertical lines—the principal emission lines of the quartz-mercury are in this region. The height of the line is proportional to the intensity (data from McAlister, 1933, for a quartz-mercury arc operated at 150 V., 4.5 A.).

using a single filter consisting of a piece of ordinary window glass. The common window glass which appears green when viewed edge on is of fairly uniform spectral transmittency, cutting off the shorter wave lengths at approximately the point where the photo-sensitivity of normal skin ends, i.e., about 3200 Å (see figure 2). If the lesions may be reproduced by radiations passing through window glass, an abnormal photosensitizer may be assumed to be present. If, as in the present case, the patient is hypersensitive to direct quartz-mercury arc radiation but not to that part of such radiation which passes through window glass a hypersensitivity of the normal photodermal mechanism is probably involved. If window glass or any other filters are used in such tests, their spectral transmission should be carefully determined. This may be very

well accomplished after the completion of the experiments, as happens to have been done in the present case; thus no time need be lost in making the observations.

Since in the present study the lesions were reproduced by quartz-mercury arc radiation, it did not appear important to examine carefully the effects of the spectrum not emitted by this source, the principal lines of which are shown in figure 2 (only a part of the visible spectrum is shown in the figure, the remainder being of no particular interest to the present study). However, an area of the patient's back was exposed to direct sunlight for a period of 20 minutes on one occasion, but without eliciting any skin changes. Sunlight does not as a rule contain enough radiation shorter than 3200 Å to produce erythema in normal skin in this period of time, but the quantity of nearer ultraviolet and visible radiation is many times greater than that obtained from the mercury arc.

All of the experimental results are summarized in table 1.

TABLE I

Source	Exposure time	Filter	Wave lengths transmitted by filter†	Response
Quartz-mercury arc*	3 min.	None	All	Severe erythema‡
" " "	3 min.	970	2600 and longer	Mild erythema
" " "	15 min.	774	3000 and longer	None
" " "	15 min.	Window glass	3200 and longer	None
" " "	15 min.	385	3500 and longer	None
" " "	15 min.	038	4300 and longer	None
Sun	20 min.	None	All	None

* Hanovia Alpine Sun type, operating on a line voltage of 220 V.
† Only wave lengths in the ultraviolet and visible are considered.
‡ Subsequently developing into an erythematous dermatitis persisting for several days.

DISCUSSION

Naturally occurring porphyrins are under suspicion as photosensitizers in man. In fact, this suspicion seems to have crystallized into the belief that porphyrins are *the* sensitizers in all cases of photosensitivity, and statements to this effect are quite common. We cannot find space here to discuss the origin of this idea, but only to say that the status of porphyrins as sensitizers in abnormal light sensitivity is not completely understood.

It will be of interest to consider the possible relation of porphyrin to the present case. Landry's syndrome is an ascending paralysis which, according to Drake (1935), may have either a toxic or an infectious background; it does not appear to be a single disease entity. In a certain number of such cases porphyrin appears in the urine (see Mason et al., 1933), and there is reason to think that it would be more often found if careful search were made. Although we did not demonstrate porphyrinuria in our case, there is no reason to believe that porphyrin or porphyrinogen might not have been found if more and larger urine samples had been examined. Had we found porphyrin, we might have placed this case together with those of Mason, particularly since the patient was a woman, and 90 per cent of the cases of Landry's paralysis with porphyrinuria

are women (Mason et al., 1933). Porphyrin is found associated with a certain proportion of cases of *Hydroa Vacciniforme seu Aestivale* (17.5 per cent according to an analysis by Senear and Fink, 1923), which is a condition of abnormal sensitivity to light resulting in severe and often disfiguring lesions of the exposed parts. It has also been found in other cases of photosensitivity displaying other kinds of lesions (Barber, Howitt and Knott, 1926; Goekerman, Osterberg and Sheard, 1929). Furthermore, it has been demonstrated that porphyrins are photosensitizers for a wide variety of living systems (see Blum, 1932 or 1935, for an account of this type of photosensitization). Meyer-Betz (1913) produced general photosensitization in himself by the injection of a rather large dose of hematoporphyrin, and Duke (1923), Frei (1926), and Blum, Watrous and West (1935) produced local photosensitivity in human skin by the intradermal injection of this pigment. After a brief consideration of this evidence, one might seem justified in jumping to the conclusion that the sensitivity to light in the present case is the result of the presence of a porphyrin acting as a photosensitizer. In fact, this exact line of reasoning has been often followed. However, there is a very strong case against porphyrin as a sensitizer in the present instance, and we should probably find the same to be true of many others if the proper experimental evidence had been obtained. For this reason, we will consider the opposing evidence at some length.

In order for a substance to act as a photosensitizer it must absorb radiation, and it can only absorb those wave lengths which fall within its characteristic absorption spectrum. Thus the absorption spectrum of a substance should show approximately the wave length region in which it may act as a sensitizer.* While the porphyrins differ in the finer structure of their absorption in the visible region they all show a strong absorption just at the borderline between visible and ultraviolet, with a maximum at about 4000 Å. This absorption falls off to minima at about 3000 Å on the ultraviolet side, and at about 4500 Å on the visible side. Examination of the data of Hausmann and Krumpel (1927), and of Clar and Haurowitz (1933), will show the similarity of the absorption spectra of the different porphyrins in this region and that it is not greatly affected by the solvent. The spectra in the visible region vary much more for the different porphyrins, but according to the data of Clar and Haurowitz the visible absorption is very much less than that in the ultraviolet. The data of Hausmann and Krumpel would indicate a much greater absorption in the visible, but it is probable that no correction for the characteristics of their photographic plates was made in preparing their figure, so that their measurements are not quantitatively correct. Their data are nevertheless valuable in giving a comparison of the approximate positions of the absorptions of a number of different porphyrins.

The absorption spectrum of a typical porphyrin in the ultraviolet region is shown in figure 2, and it may be seen at a glance that there is no agreement between this curve and the sensitivity of our patient. In fact, our patient was sensitive in a region at which a minimum in the absorption spectrum of hematoporphyrin occurs. Furthermore, the experiments of Hausmann and Sonne (1927) and of Hausmann and Kuen (1933) on the sensitization of erythrocytes by porphyrins also demonstrate experimentally that these substances do not sensitize in the region of the normal erythemic response, with the exception of

* A corollary of the Grotthus-Draper law, the first law of photochemistry.

mesoporphyrin, which may show some sensitizing effect in this region, but also exhibits very strong sensitization in the nearer ultraviolet and visible (Hausmann and Kuen). We have found that when the skin is sensitized locally by intradermal injection of hematoporphyrin, the response to sunlight is of the same magnitude when a filter of window glass is interposed as when exposed directly to the sun. Thus all the evidence points to the fact that the wave lengths to which porphyrins sensitize do not correspond at all with those to which our patient was sensitive.

It was suggested that the sensitization might be the result of the quinine which was given the patient some time before she entered the hospital, and to which she responded with a marked dermatitis, not, however, limited to the exposed parts as was the later dermatitis which we observed. Quinine has been stated to be a photodynamic photosensitizer by some investigators, but Frei (1926) was unable to obtain sensitization of the skin to sunlight by the intradermal injection of this drug. The absorption spectrum of quinine (Hicks, 1930; Heidt and Forbes, 1933) indicates a very considerable absorption of radiation between 3000 Å and 4000 Å; the absorption shorter than 3200 Å is considerable, but if one examines the transmittance of skin as shown in the curves of Bachem and Reed (1931) one finds that the transparency of the epidermis falls off very rapidly below 3500 Å which would tend to limit the sensitizing power of quinine in the region to which our patient demonstrated her greatest sensitivity, i.e., below 3200 Å. From a consideration of these data it appears that if quinine were the sensitizer in the present case, the patient should react to radiation much longer than that to which she is sensitive, and should be more sensitive to radiation longer than 3200 Å, than to radiation shorter than this limit. Thus, if quinine was an etiological factor in the sensitivity of the skin to light it must have acted to enhance some part of the normal photosensitive mechanism, not as a specific photosensitizing substance in the skin.

The response of normal skin to light must be rather complex. There must be first a photochemical reaction, the products of which bring about dilation of the small vessels in the skin, which is observed as erythema, and subsequently pigmentation. The steps involved may be even more numerous, and we must assume that there are a number of parts in the whole system, the hyperactivity of any one of which might result in an enhanced erythemic response. Thus it is not surprising to find that a profound and general nervous disturbance of the type occurring in our patient should be accompanied by a sensitivity to light, as the normal erythemic mechanism must be affected by any disturbance in the control of the minute vessels; nor again where the administration of a drug produced marked skin changes. Such an enhanced response would, of course, be produced by the same wave lengths as the normal response, and it is probable that many cases of abnormal sensitivity to light are of this type. The group of individuals (" vegetativ Stigmatisierten ") whom Ellinger (1932) found to show a greater sensitivity to quartz-mercury arc radiation than normals, may probably be placed in this group. He believes this condition to be associated with thyroid gland disturbance. We see no reason, however, for believing that the thyroid gland is directly involved in the photosensitivity of our patient, but the possibility cannot be excluded. On the other hand, a number of cases have been reported in which the sensitivity lies in a wave length region outside of the normal and in which an abnormal sensitizer must be present. The cases of

Urticaria solare described by Duke (1923), Vallery-Radot et al. (1926, 1928), Frei (1925), and Blum, Allington and West (1935) offer examples of the latter type, as does also the condition described by Urbach and Konrad (1929), and in all probability there are others. The position of Hydroa would seem to be questionable (see Gottron and Ellinger, 1931) and it may well be that the etiology is not the same in all the cases described under this name. Conditions involving abnormal sensitivity to light can be properly characterized only when wave length studies are carried out and it is to be hoped that these will be more frequently made in the future than in the past. We may point out that the same treatment would hardly be expected to succeed in cases of all types.

Summary

1. A condition of abnormal sensitivity to light in a case of ascending paralysis, manifesting itself as an erythematous dermatitis on the face, hands and arms, is described.

2. Quartz-mercury arc radiation produced a much more severe, and persistent erythema in the skin of this patient than in normal skin, and this took on the appearance of the erythematous dermatitis displayed by the patient.

3. Only that portion of the mercury arc radiation shorter than 3200 Å was active in eliciting this erythema. The sensitivity would thus seem to be restricted to the same wave length region as the erythemal response of normal skin, and the condition could best be explained as a hypersensitivity of some part of this mechanism.

4. It is pointed out that porphyrins or quinine cannot be suspected as photosensitizers responsible for this condition.

5. The relationship to other types of photosensitivity is discussed.

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EDITORIAL

ADRENAL ATROPHY AS A CAUSE OF ADDISON'S DISEASE

Various pathologists [1, 2] have drawn attention recently to the increasing frequency with which adrenal atrophy is found as the causative lesion in Addison's disease. It was formerly estimated that atrophy was found in only about 10 per cent of the autopsies of cases of Addison's disease and tuberculosis of the adrenals in the other 90 per cent. However in recent years, as pointed out by Wells,[1] series of cases have been reported in which atrophy was found in as high as from 30 to 50 per cent of the instances.

In Brenner's review of the subject he pointed out the chief features of adrenal atrophy. It is a non-inflammatory process, including necrosis of either the adrenal cortex alone or of the cortex and medulla, followed by a disappearance of the necrotic tissue with a corresponding shrinkage of the adrenal. Ineffective regenerative changes are observed. In the type most commonly found associated with Addison's disease it is the cortical zone which has largely disappeared leaving the medulla relatively intact.

Since in the type of tuberculosis of the adrenal which is found as a cause of Addison's disease both the cortex and the medulla are usually destroyed, it might be supposed that clinical distinctions would be found to correspond with these variations in the tissue involvement accompanying these two etiologic types of Addison's disease. Wells raises the question whether longer duration and a less pronounced hypotension may not characterize the cases due to purely cortical deficiency. The matter is, however, by no means definitely settled.

The nature of the process which results in the necrosis of the adrenal cortex, with or without some medullary damage, is still quite undetermined. It is well known, however, that in experimental animals the adrenal cortex is very susceptible to bacterial toxins such as diphtheria toxin and also that human cortical tissue will show evidence of damage in all cases that have died as a result of acute infections. Basic studies establishing this fact were those of Dietrich [3] during the World War. This investigator utilized the opportunities of examining healthy human glands from those who had met sudden death. With these he compared the glands removed from a series of cases in whom wound infection was the cause of death. The cortical tissue in these latter uniformly showed destructive changes.

Such cortical damage in infectious diseases is probably repaired rapidly as a rule since the cortical cells and especially those of the *zona glomerulosa* are capable of rapid regeneration. Such regeneration is readily observed in

[1] Wells, H. Gideon: Addison's disease with selective destruction of the suprarenal cortex, Arch. Path., 1930, x, 499–523.

[2] Susman, Wm.: Atrophy of the adrenals and Addison's disease, Endocrinology, 1936, xx, 383–388.

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experimental animals. How frequently residual atrophy remains is not known.

In certain dramatic instances the damage to the adrenal in infections consists of massive hemorrhage with disintegration of the glands. These cases are marked by skin hemorrhages, vasomotor collapse and early death. The syndrome is associated especially with the onset of meningococcus infections, less frequently with those due to the pneumococcus.

No conclusive study in humans has yet shown how large a part in the clinical phenomena of acute infections may be played by less extensive forms of damage to adrenal cortical tissue. It might well be of course that such damage might result in a mingling of symptoms of acute adrenal insufficiency with those due to the other results of the infection. Moreover, besides this obvious possibility, it must be recalled that the adrenal bears some relation to bodily resistance to infection the nature of which is by no means clear. Both adrenalectomized animal and human cases of Addison's disease become abnormally susceptible to the effects of infections, and to the action of bacterial toxins and of certain poisons. Moreover it seems possible that the adrenal cortex as a storage place of cevitamic acid, which has been shown to be capable of stimulating antibody formation, plays still another rôle in connection with the bodies' response to acute infectious disease.

Susman has raised the question whether repeated past infections or poisonings may not account for the multiple atrophic spots he has noted in the adrenal cortex of some autopsy cases and suggests that possibly in susceptible individuals, more extensive damage of this kind might eventually lead to such complete cortical atrophy as would cause Addison's disease.

Another explanation of chronic cortical atrophy has appealed to Wells.[4] He has several times drawn attention to the similarity between the pathologic cellular necrosis in cortical atrophy and that which is seen in acute yellow atrophy of the liver. Both, Wells feels, are best described as toxic cellular necrosis. Wells is inclined to carry the parallelism further and to suggest that, just as the increase of acute yellow atrophy was probably attributable to poisons such as cinchophen, so there might also be found a poison responsible for the apparent increase in the number of cases of adrenal cortical atrophy. Recently Wells encountered a case of cortical atrophy probably due to the therapeutic use of *germanin* and was able to show that this drug has a fairly specific damaging effect upon the adrenal cortex of laboratory animals.

It seems apparent that this suggestion is one which clinicians should bear in mind in investigating the history of patients with Addison's disease.

M. C. P.

[4] Wells, H. Gideon, Humphreys, Eleanor M., and Work, Emma G.: Significance of the increased frequency of selective cortical necrosis of the adrenal as a cause of Addison's disease, Jr. Am. Med. Assoc., 1937, cix, 490–493.

REVIEWS

Bright's Disease and Arterial Hypertension. By WILLARD J. STONE, B.Sc., M.D., F.A.C.P., Clinical Professor of Medicine, University of Southern California. 352 pages; 16.5 × 24 cm. W. B. Saunders Co., Philadelphia. 1936. Price, $5.00.

This volume opens with brief historical sketches of those whose names have been associated with studies in the field of renal disease. Then follow chapters on classification of renal disease (the author presents a modification of the classification of Volhard and Fahr), renal physiology, water balance, edema, renal function tests, uremia, etc. These chapters constitute too briefly stated reviews of the more prevalently accepted current theories. There is little or no critical discussion and the author offers little in the way of personal opinion. Subsequent chapters deal with "Acute Hemorrhagic Bright's Disease, Second Stage Hemorrhagic Bright's Disease, Terminal Stage Hemorrhagic Bright's Disease, Acute and Chronic Degenerative Bright's Disease." Forty-four pages are devoted to arterial hypertension, arteriosclerosis and arteriosclerotic Bright's disease. This latter subject is divided into latent and active forms by the author. The second part of the title seems scarcely justified by the amount of discussion given it as such. The 140 autopsied cases of Bright's disease are abstracted too briefly to be very instructive.

W. S. L., JR.

Dextrose Therapy in Everyday Practice. By E. MARTIN, Sc.D. 451 pages; 16 × 24 cm. Paul B. Hoeber, Inc., New York. 1937. Price, $3.00.

An impersonal digest of significant dextrose literature since 1900, this readable book correlates experimental laboratory and clinical findings with admirable brevity. More than a handbook, it succeeds in giving a dextrose-eye view of metabolism without losing yardage in controversy or flight of fancy. The first portions dealing with chemistry and physiology show occasional proof-reader's errors (*normal blood sugar range is from 0.8 to 0.12*) which tend to shake faith in figures quoted which are less familiar. The author is strict enough too in insisting on the substitution of chemically correct *dextrose* for the familiar *glucose* of common parlance. Yet later on he uses *glycolysis* where *glycogenolysis* is apparently meant. The latter portions of the book show the difficulty of the pure-scientist-in-medicine's uncritical acceptance of medical literature at its face value (as where on p. 110 he so glibly speaks of *simple blockage of the reticuloendothelial system.*) His therapy has a Gould and Pyle-ishness throughout that is most dangerous in the genito-urinary section where he is still in the intravenous mercurochrome era. The charts are good, and the pictures better than average. Definitely a transition book, it would interest the clinically-minded second-year, and the chemically-minded third-year medical student, and be helpful provided that the student remembers that dextrose is but one of many therapeutic agents.

C. A.

Gastroscopy: The Endoscopic Study of Gastric Pathology. By RUDOLF SCHINDLER, M.D. 343 pages; 17.5 × 25 cm. University of Chicago Press, Chicago, Ill. 1937. Price, $7.50.

Every chapter in the book is full of valuable information. The technic of gastroscopy is clearly and concisely stated. The splendid description of the procedure will be extremely helpful to those who desire to do gastroscopy. To those not desir-

ing to do gastroscopy, it will materially broaden their knowledge of the technical side of the procedure. When technical problems do occur, they are comparatively easy to overcome if one follows the directions as outlined in the chapter on technic. The reviewer has followed very closely the technic as outlined, and has found it most satisfactory. The position of the patient for emptying the stomach is of the utmost importance, and this has been stressed by the author. Likewise, the orientation of the instrument in the stomach has been described thoroughly. This, of course, is very necessary, so as to be able at all times to know which portion of the stomach is being observed.

Many diagrams have been used to show the portion of the stomach visualized, with the instrument at different levels, and when the instrument is rotated in different positions. Great detail concerning orientation is of the utmost importance. The technic of introducing the gastroscope can be mastered in a very short time, but to be able to determine accurately the portion of the stomach under observation, requires a great deal of training. The gastroscopic appearance of the normal stomach is extremely well presented. After all, one must be perfectly familiar with the picture of the normal stomach before attempting to study gastric pathology.

In the study of gastric pathology, the author stresses two important diagnostic procedures, namely: roentgen-ray relief studies, and gastroscopy. Both have a definite place in the diagnosis of gastric lesions. The two methods bear a supplementary relation to each other. Certain facts may be obtained by one procedure, and other very definite facts obtained by the other.

The author definitely favors gastroscopy in studying the different types of gastritis. His classification of the different types of gastritis is all that can be desired; the different types are easily recognized gastroscopically. In the diagnosis and treatment of gastric ulcer, the author stresses the importance of gastroscopy, and urges the advantage of frequent gastroscopic examinations to determine what results are being obtained from treatment. In the diagnosis of carcinoma, he believes a positive diagnosis can be made by roentgen-ray relief studies and gastroscopy. He does not believe there is any necessity for surgical exploration of the abdomen in any case in order to make the diagnosis. He makes a strong plea for roentgen-ray relief study and thorough gastroscopic examination, and states that the two methods of examination will give one the correct diagnosis in almost every case. The reviewer believes that in order to make the diagnosis of carcinoma by these two methods alone, one must have had a vast amount of experience in gastroscopy, and in the interpretation of roentgen-ray relief studies. In determining the etiology of obscure gastric hemorrhage, the great advantages of gastroscopy have been thoroughly discussed.

In addition to the clear and concise manner in which gastroscopy has been discussed, the book contains a very complete bibliography of the subject, and 96 perfectly splendid color plates. One not familiar with gastroscopy might be inclined to doubt the brilliant colors found in the plates. The reviewer, however, from his own experience, believes that the colors are not exaggerated, but quite clearly represent different phases of gastric pathology. With each color plate, there is a short discussion of what it represents.

The book should be of real value to every internist, and especially to those limiting their practice to gastroenterology. It is of course, of the utmost value to those interested in gastroscopy. The reviewer is of the opinion that gastroscopy as a diagnostic procedure is just as valuable as the roentgen-ray, in the diagnosis of gastric pathology. It in no way replaces roentgen-ray studies—they both bear a supplementary relation to each other.

E. B. F.

Endocrinology: Clinical Application and Treatment. By AUGUST A. WERNER, M.D., F.A.C.P. 672 pages; 15 × 24 cm. Lea and Febiger, Philadelphia. 1937. Price, $8.50.

Quite a number of texts on endocrinology have been published within the past few years. On greeting a new publication one is interested to see how it differs from, or what it adds to, those already available.

This particular work contains many valuable data amassed from the author's large practice and wide experience. There are many case reports and many illustrations. The classical endocrine syndromes are well delineated.

In the opinion of the reviewer, the book is marred somewhat by the enthusiastic inclusion of many conditions of unknown origin as of probable or possible endocrine etiology.

The illustrations in general are excellent but there are included some of questionable choice, notably that illustrating lipodystrophia progressiva, a very good photograph of a very fat woman but lacking the essential characteristic of this rare anomaly, namely, the remarkably complete emaciation above the waist.

The book gives a good idea of the methods of practice of an enthusiastic and well informed endocrinologist.

T. P. S.

The Digestive Tract: A Radiological Study of Its Anatomy, Physiology and Pathology. By ALFRED E. BARCLAY. 427 pages; 19 × 25 cm. Cambridge University Press Department, Macmillan Co., New York. 1937. Price, $12.00.

A striking feature of this book is that the author obviously considers an understanding of the normal, an essential prerequisite to the evaluation of pathological change, since he devotes roughly the first half of his book to anatomy and physiology from the point of view of the radiologist. Included in this discussion are summaries of some of the latest researches on the digestive tract.

The book is divided into three main parts. Part I is devoted to technic including not only a careful review of routine measures employed in the practice of radiology but also stressing some of the dangers associated with this work. The completeness and the clarity of Part I set a high standard.

In Part II, devoted to the radiological examination of the "normal" gastrointestinal tract, the first section includes a discussion of the anatomy of the "normal" stomach and the inherent mobility and adaptability of the abdominal viscera. In this section the alimentary tract is considered as a whole and the justifiable conclusion is reached that an alimentary tract may approximate the average, but that there is no fixed standard of normality. The factors influencing the form and position of the stomach, the effects of posture and respiration and the mobility and adaptability of the viscera are discussed in detail.

Section II of Part I, devoted to physiology, reviews the movement of food from mouth to anus as observed by the radiologist. The process of swallowing, gastric peristalsis, pyloric sphincter activity as well as the intestinal movements, are all portrayed radiographically. The author's discussions are thought-provoking as can be seen from his statement that gravity and tonic action appear to play a part in the control of the pyloric sphincter but that the peristaltic waves seem to be identical whether the sphincter relaxes or not. Moreover, he is certain that the opening of the pylorus does not depend on the acidity or alkalinity of the food.

On the basis of this thorough presentation of anatomy and physiology the author develops Part III which is devoted to pathology. From the esophagus and through the colon, in logical sequence, the reader has presented to him a fascinating discussion of "roentgenologic pathology." An excellent chapter on the gall-bladder is included.

The author never attempts to be dogmatic and often admits the inadequacies of roentgenologic diagnosis, as, for example, in his discussion of gastritis.

The last quarter of the book presents seven appendices which must be invaluable to the roentgenologist and especially to the beginner in this specialty. The bibliography is apparently up to date and the division of indices into both an author and a general index, is always a convenience to the reader.

The book represents a well written, well illustrated text which could only be the outcome of an unusual roentgenologic experience.

S. M.

COLLEGE NEWS NOTES

Gifts to the College Library

Grateful acknowledgment is made of the receipt of the following donations to the College Library of publications by members:

Books

Dr. H. A. Pattison (Fellow), Livingston, N. Y., "Potts Memorial Hospital: A Review of Activities of the First Ten Years with a Report of a Special Survey Committee";
Dr. Edward Weiss (Fellow), Philadelphia, Pa., "Practical Talks on Kidney Disease";
Dr. John Zahorsky (Fellow), St. Louis, Mo., "Baby Incubators," "Golden Rules of Pediatrics," "Pediatric Nursing" and "Synopsis of Pediatrics."

Reprints

Dr. E. J. G. Beardsley (Fellow), Philadelphia, Pa.—1 reprint;
Dr. Victor W. Bergstrom (Fellow), Binghamton, N. Y.—1 reprint;
Dr. George Blumer (Fellow), New Haven, Conn.—6 reprints;
Dr. Coursen B. Conklin (Fellow), Washington, D. C.—3 reprints;
Dr. Edward E. Cornwall (Fellow), Brooklyn, N. Y.—8 reprints;
Dr. Norbert Enzer (Fellow), Milwaukee, Wis.—1 reprint;
Major C. J. Gentzkow (Fellow), M. C., U. S. A.—1 reprint;
Dr. George T. Harding, III (Fellow), Columbus, Ohio—1 reprint;
Dr. Arthur A. Herold (Fellow), Shreveport, La.—1 reprint;
Lt. Col. Charles C. Hillman (Fellow), M. C., U. S. A.—3 reprints;
Dr. Charles E. Homan, Jr. (Fellow), Hartford, Conn.—1 reprint;
Dr. Philip B. Matz (Fellow), Washington, D. C.—1 reprint;
Dr. Warren W. Quillian (Fellow), Miami, Fla.—3 reprints;
Dr. R. J. Reitzel (Fellow), San Francisco, Calif.—1 reprint;
Dr. F. L. Roberts (Fellow), Trenton, Tenn.—1 reprint;
Dr. Edward Schons (Fellow), St. Paul, Minn.—1 reprint;
Dr. Philipp Schonwald (Fellow), Seattle, Wash.—1 reprint;
Dr. W. Warner Watkins (Fellow), Phoenix, Ariz.—2 reprints;
Dr. Clarence R. Bennett (Associate), Eufaula, Ala.—1 reprint;
Dr. John Francis Briggs (Associate), St. Paul, Minn.—7 reprints;
Dr. Hyman I. Goldstein (Associate), Camden, N. J.—1 reprint;
Dr. William H. Gordon (Associate), Boston, Mass.—2 reprints;
Dr. W. H. Griffith (Associate), Huron, S. D.—1 reprint;
Dr. Charles Solomon (Associate), Brooklyn, N. Y.—2 reprints.

Dr. Roy R. Kracke (Fellow), Emory University, Ga., has been elected a member of the American Board of Pathology for a term of six years. Dr. Kracke is also chairman of the Section on Pathology and Physiology of the American Medical Association.

Dr. William E. Robertson (Fellow), Philadelphia, is now President of the Philadelphia County Medical Society. Dr. Louis H. Clerf (Fellow), Dr. Michael A. Burns (Fellow), and Dr. Isadore Kaufman (Fellow) are directors.

Dr. E. J. G. Beardsley (Fellow), Philadelphia, is Secretary-Treasurer of the American Association of the History of Medicine.

Dr. William D. Stroud (Fellow), Philadelphia, is President of the Philadelphia Heart Association; Dr. David Riesman (Fellow), Vice President; Dr. Thomas M. McMillan (Fellow), Secretary; Dr. Edward E. Krumbhaar (Fellow), a member of its board of governors.

Dr. Ross McClure Chapman (Fellow), Towson, Md., is President of the American Psychiatric Association; Dr. J. Allen Jackson (Fellow), Danville, Pa., and Dr. Walter L. Treadway (Fellow), U. S. Public Health Service, are members of the executive committee.

Dr. Edward S. Sledge (Fellow), Mobile, Ala., is President of the Alabama State Medical Association.

Dr. Paul A. Yoder (Fellow), Winston-Salem, N. C., is President of the Eighth District Medical Society of that State.

Dr. John W. Tappan (Fellow), El Paso, Tex., has been made Health Officer of the El Paso City and County Health Unit.

Dr. Dudley C. Smith (Fellow) is President of the University of Virginia Medical Society.

Dr. Charles W. Waddell (Fellow), Fairmont, W. Va., is President of West Virginia State Medical Association; Dr. A. A. Shawkey (Fellow), Charleston, is Second Vice President and Dr. T. M. Barber (Associate), Charleston, is Treasurer.

The Fifth International Congress of Radiology was held in Chicago, September 13 to 17, with a large delegation from Europe, Mexico, Canada and South America. This was the first time the Congress has met in the United States. Dr. B. H. Orndoff (Fellow), Chicago, was Secretary of the Congress; Dr. Arthur C. Christie (Fellow), Washington, was chairman of the Executive Committee; Dr. George E. Pfahler (Fellow), Philadelphia, was an honorary vice president.

Dr. E. H. Shuller (Associate), McAlester, Okla., is President of the Southeastern Oklahoma Medical Association.

Dr. J. A. Myers (Fellow), Chief of the Chest Clinic at the University of Minnesota and President of the National Tuberculosis Association, will be the guest speaker at the Post-Graduate Course on Tuberculosis to be conducted in Oklahoma City, October 13.

Dr. Clarence H. Webb (Fellow), Shreveport, La., is President of the Louisiana State Pediatric Society.

Dr. Horace W. Soper (Fellow), Dr. Frank D. Gorham (Fellow) and Dr. Lee Pettit Gay (Fellow), all of St. Louis, are President, Vice President and Treasurer, respectively, of the Missouri Society for the Advancement of Gastro-enterology.

Dr. Henry K. Speed (Fellow), Sayre, Okla., is President-Elect of the Oklahoma State Medical Association.

Dr. O. B. Kiel (Fellow), Wichita Falls, Tex., is President of the Texas State Board of Medical Examiners.

Dr. Edward H. Schwab (Fellow), Galveston, Dr. M. D. Levy (Fellow), Houston, and Dr. Robert M. Barton (Fellow), Dallas, are President, Vice President and Secretary-Treasurer, respectively, of the Texas State Heart Association.

Dr. Bedford Shelmire (Fellow), Dallas, is President of the Texas Dermatological Association.

Dr. John G. Young (Fellow), Dallas, is President of the Texas Pediatric Society.

Dr. John A. McIntosh (Fellow), San Antonio, is Second Vice President of the Texas Neurological Association.

Dr. May Owen (Fellow), Fort Worth, Tex., recently received the honorary degree of Doctor of Science, conferred by the Texas Christian University.

Dr. Edward J. Van Liere (Fellow), Morgantown, has been appointed Dean of the West Virginia University School of Medicine.

Dr. Ernest D. Hitchcock (Fellow), Great Falls, is Vice President of the Montana State Medical Association.

Dr. David Riesman (Fellow), Philadelphia, emeritus professor of clinical medicine and professor of the history of medicine, University of Pennsylvania School of Medicine, was recently the recipient of the honorary degree of Doctor of Laws, conferred by the University of Wisconsin.

Dr. Jacob C. Geiger (Fellow), Director of Public Health for the City and County of San Francisco, was recently elected President of the Pasteur Society of Central California.

Dr. Russell H. Oppenheimer (Fellow), Dean of Emory University School of Medicine and heretofore Superintendent of Emory University Hospital, Atlanta, has been made Medical Director of the Hospital.

Dr. Hugo A. Freund (Fellow) was recently appointed a member of the Public Welfare Commission of Detroit.

Dr. James J. McGuire (Fellow), Trenton, is Secretary of the New Jersey State Board of Medical Examiners.

Dr. William de B. MacNider (Fellow), Chapel Hill, Kenan Research Professor of Pharmacology at the University of North Carolina School of Medicine, has recently been appointed Dean, to succeed Dr. Charles S. Mangum.

Dr. Robert Finley Gayle, Jr. (Fellow), Richmond, is one of the physicians ap-

pointed to a new board created to have supervision over state mental hospitals in Virginia.

Dr. Charles E. Sears (Fellow), Portland, Ore., was elected President of the Pacific Northwest Medical Association during July.

Dr. T. Grier Miller (Fellow), Philadelphia, Professor of Clinical Medicine in the University of Pennsylvania School of Medicine and Chief of the Gastro-Intestinal Section, Hospital of the University of Pennsylvania, will have charge of the newly established "Kinsey-Thomas Foundation for the Study and Treatment of Diseases of the Digestive System" at the University of Pennsylvania. The late Miss Frances T. Kinsey provided $200,000 in her will for the establishment of the Foundation.

The estate of the late Dr. James M. Anders (Master), Philadelphia, amounting to over $500,000, has been ordered distributed. Dr. Anders' will provided bequests of $2,000 to the Philadelphia County Medical Society Library Fund and $1,000 to the Society's Aid Association. It also provided $2,500 for the Board of Directors of the Philadelphia County Medical Society to be held in trust and to be used to meet the expenses of the Philadelphia celebration of the Annual Health Day, a project in which Dr. Anders was deeply interested and which he founded. The residuary estate was left in trust, the income to go to Mrs. Anders for life. When the trust is ended, $50,000 is to go to the trustees of the University of Pennsylvania for the Endowment Fund of the Graduate School of Medicine of the University.

Dr. Thomas B. Magath (Fellow), Rochester, Minn., has been chosen President-elect of the American Society of Clinical Pathologists.

Under the presidency of Dr. J. Morrison Hutcheson (Fellow and Governor), Richmond, the Medical Society of Virginia will hold its annual meeting in Roanoke, October 12 to 14. Among the invited guests are Dr. Russell L. Cecil (Fellow), New York City, and Surgeon General Thomas Parran (Fellow and Governor), of the U. S. Public Health Service.

Dr. George B. Lawson (Fellow), Roanoke, was recently reappointed by the Governor as a member of the State Board of Health, his term of office to continue until 1942.

Dr. Louise Tayler Jones (Fellow), McLean, Va., one of the Vice Presidents of the Medical Women's International Association, attended the Fourth Congress held in Edinburgh, Scotland, July 13 to 18.

Dr. Elizabeth Bass (Fellow), New Orleans, La., attended the Medical Women's International Association in Edinburgh, Scotland, July 13 to 18, as a councillor from the American Medical Women's Association.

The degree of Doctor of Laws was conferred upon Dr. C. C. Bass (Fellow), Dean of Tulane University School of Medicine by Duke University at the annual commencement, June 7.

The Southern Tuberculosis Conference will hold its annual meeting at the John Marshall Hotel, Richmond, Virginia, September 29, 30 and October 1, 1937. Among the speakers will be Paul H. Ringer, M.D. (Fellow), Asheville, North Carolina; J. A. Myers, M.D. (Fellow), University of Minnesota; Louis Hamman, M.D. (Fellow), Johns Hopkins School of Medicine; Horton Casparis, M.D. (Fellow), Vanderbilt University School of Medicine; L. J. Moorman, M.D. (Fellow), Oklahoma City.

OBITUARIES

DR. JOSEPH LEGGETT MILLER

Dr. Joseph Leggett Miller (Fellow), Chicago, Ill., died near Great Falls, Montana, on August 6. Death was sudden. He had gone to Montana on his annual vacation. Dr. Miller was a native of Kewanee, Illinois, where he was born November 24, 1867. He received his Bachelor's degree from the University of Michigan in 1893. Two years later he graduated in Medicine at Northwestern University Medical School. He served his internship at Mercy Hospital in Chicago, and then became associated with Dr. Frank Billings.

Dr. Miller became a teacher at Rush Medical College in the Department of Medicine, eventually becoming Professor of Medicine. Since 1924 he was Clinical Professor of Medicine at the University of Chicago. For years he was a member of the Attending Staff at the Cook County Hospital. For some time he served as president of the Staff. For many years he was Attending Physician at St. Luke's Hospital.

He was a member of the American Medical Association, having served as secretary of the section on Practice of Medicine for five years, and as chairman of the same section in 1908–1909. He was a member of the Association of American Physicians, the American Society for Clinical Investigation and the Central Society for Clinical Research. He was a member of the Chicago Society of Internal Medicine, which he once served as president. Likewise he was a member and past president of the Chicago Institute of Medicine. He was also a member of the Chicago Medical Society and the Illinois Medical Society. He had been a member of the American College of Physicians since 1929.

He served in the World War, first as Major and later as Lieutenant Colonel in the Medical Corps. For many months he was chief of the Medical Department at Camp Dodge. From 1909 until 1931 he was Editor-in-Chief of the Archives of Internal Medicine. He also contributed largely to medical literature. Dr. Miller had a wide reputation as a teacher and investigator and a contributor to the literature. He had a great gift for friendship; he was widely known, admired and beloved, unassuming and frank in conversation, exceptionally clear and direct in his teaching, a genial companion and loyal friend, and a physician who exemplified the old virtues of which the profession is so proud.

JAMES G. CARR, M.D., F.A.C.P.,
Governor for Northern Illinois.

DR. JUDSON DALAND

The death of Dr. Judson Daland (Fellow) of Philadelphia on August 14, 1937, at 77 years of age removes a well known, distinguished and

picturesque personality from the medical profession and from the citizenry of his adopted city and state.

Dr. Daland had been in ill health for two years, as the result of an automobile accident in England and from a subsequent major operation, and his passing was a happy release from increasing infirmities. Born in New York, in 1860, Judson Daland attended the medical school of the University of Pennsylvania and graduated in 1882. Shortly after his graduation he established his practice in Philadelphia and began forming the professional associations of a long and active life.

He was, from his earliest years, deeply interested in all aspects of science, especially biological science, and soon became interested in teaching and, early, affiliated with the Medico-Chirurgical Medical School and Hospital. Revealing his ability, talent and worth as a medical practitioner, investigator, teacher and writer Dr. Daland was advanced in teaching positions until he became, in 1903, the Professor of Clinical Medicine in the Medical School and Attending Physician to its Hospital. Judson Daland's greatest contribution to clinical medicine was in emphasizing and reëmphasizing the direct relationship of focal infections in the teeth, tonsils and sinuses to local (and frequently misunderstood) symptoms and to the general health conditions of patients at a period in medical history when such a relationship was denied, ignored and, all too often, derided by the majority of the, so termed, leaders of the medical profession. Dr. Daland was, from his earliest years in medicine, deeply interested in tropical diseases and pursued knowledge in this subject in many lands. He was one of the earliest observers to point out that tropical diseases were to be found remote from the tropics and he had many opportunities of illustrating the truth of his statement by demonstrating patients in his Philadelphia clinic that were suffering from such maladies as pellagra, sprue, yaws, filariasis, beri-beri, quartan malaria and leprosy. In no Philadelphia clinic of that period was as much attention given to the seldom encountered disorders as was true in Dr. Daland's service and the reason for this is to be found in Dr. Daland's frequent visits to the tropical countries and his entire familiarity with the diseases of those sections.

During Dr. Daland's active professional life he was a much sought consultant and served in such a capacity in a number of the city's and state's hospitals.

When the Medico-Chirurgical Medical School merged with the Medical School of the University of Pennsylvania to become the Graduate School of that great institution Dr. Daland became a Professor of Clinical Medicine in the Graduate School and continued this association until his retirement from practice when he became Emeritus Professor of Clinical Medicine.

Dr. Daland was an exceptional man in the medical profession for, in addition to being a nationally and internationally recognized expert in medical science, he was, perhaps, even better known as a world traveller,

an archeologist, a paleontologist, a connoisseur of art, a musician of ability, an accomplished linguist and a sportsman well known in many of the obscure corners of the world. In recent years Dr. Daland has devoted much time and thought to the activities of the Philadelphia Institute for Medical Science, now active within the walls of the Philadelphia General Hospital, of which organization he was one of the founders and its first president and to which, it is said, he has bequeathed his $200,000 estate.

Dr. Daland represented an unusual type of a rapidly passing generation. Is it not possible that his life, his experiences, his education, that continued to the very end of his life, hold a lesson for the members of a younger generation?

Here was a physician who possessed an exceptional education in medicine and in life. He was cultured, travelled and truly learned but the more he knew the more modest he became concerning his many accomplishments and the more conscious he was of his ignorance concerning many of life's secrets. It is said that he wished his ashes to be placed in an urn in the Philadelphia Philosophical Society's rooms where he had spent so many pleasant hours and that upon the urn he wished placed the words, "I sought Truth."

Could any physician desire a better epitaph?

E. J. G. Beardsley, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania

DR. ELMER L. EGGLESTON

Dr. Elmer L. Eggleston (Fellow), Battle Creek, Mich., died after three days' illness, July 7, 1937, of coronary thrombosis.

He was born in Marion, Iowa, in 1874. He received his M.D. degree from American Medical Missionary College (Chicago), 1900. He did post-graduate work at the New York Post-Graduate Medical School in Vienna. At the time of his death, he was head of the Department of Internal Medicine, Group B, Battle Creek Sanitarium. He was the author of several published articles, usually pertaining to gastroenterology. Dr. Eggleston was a member of the Northern Tri-State Medical Society, Mississippi Valley Medical Society, Calhoun County Medical Society, Michigan State Medical Association, and a Fellow of the American Medical Association. He was elected a Fellow of the American College of Physicians on April 6, 1922.

His medical career was entirely devoted to institutional work at the Battle Creek Sanitarium, having taken his internship there and followed as assistant physician and finally head of the above mentioned department. For approximately 20 years he devoted himself largely to the subject of gastroenterology. Dr. Eggleston possessed an unusual personality and with it went a keen mind and a sympathetic character, which fitted him so admirably for his medical career. During his years of work he met a great many prominent people from all parts of the United States, all of whom

became his devoted friends. They all appreciated his sympathetic personal devotion to them. He had an aptness for recognizing not only their physical ills, but also was able to help them adjust themselves to any complexes they might have established as a result of anxiety, worry and trouble. Each year he witnessed the return of old patients and many patients referred by Doctors and friends, which proved above everything else his success as a physician. He had many local friends and patients who leaned heavily on him and his death was a shock to not only these, his friends and neighbors, but to former patients in all parts of the country. Scores of telegrams and floral tributes further proved the love and esteem of those that knew him.

A paragraph from an editorial portrays Dr. Eggleston as he was known at home: "The professional loss through Dr. Eggleston's passing will be widely recognized. But Battle Creek, to which he belonged and into which he built the strong attachments of Home, grieves for the loss of a friend and fellow citizen who made himself endeared here because, in so many ways of helpful service, he had practiced that philosophy which he gave to the troubled patients—and had made the most of his todays."

M. A. MORTENSEN, M.D., F.A.C.P.

DR. JACOB FOWLER AVERY

Dr. Jacob F. Avery, a Fellow of the College, died at La Jolla, California, June 25, 1937. Dr. Avery had been retired from active practice for the past four years due to coronary disease, which resulted in his death.

Dr. Avery was born at Poughkeepsie, New York, January 19, 1873. He was graduated from Minneapolis Central High School in 1892 and from the University of Minnesota, College of Medicine, class of 1899. Following his internship at the City Hospital (now Minneapolis General Hospital), Dr. Avery practised in Virginia and Aitken, Minnesota before locating in Minneapolis in 1906. He retired from active practice in April 1932.

Dr. Avery was elected to membership in the Hennepin County Medical Society December 3, 1906. He became an Emeritus member in 1933 and an affiliate member of the Minnesota State Medical Association the same year.

He was married to Mary L. Esmond, June 4, 1902, who, with one son, Esmond Avery, of Detroit, Michigan, survives him.

Dr. Avery was commissioned a Captain in the Medical Corps, U. S. Army, July 10, 1917, and served with the 44th Infantry and the 39th Field Artillery at Camp Lewis, Washington. He was discharged at Camp Dodge, Iowa, October 14, 1919. For two years he served as chief of Medical Hospital Service in Minneapolis (this was forerunner of the Veterans' Administration).

He was a Fellow of the American College of Physicians and, until his

retirement, a member of the Minnesota Society of Internal Medicine. In Minneapolis he was a member of the staffs of Northwestern Hospital and Abbott Hospital.

JAMES F. CHURCHILL, M.D., F.A.C.P.,
Governor for Southern California

DR. FRANK ALSWORTH WAPLES

Dr. Frank Alsworth Waples (Fellow), Houston, Texas, died March 3, 1937. He was born in New Orleans, Louisiana, in 1868. He held the degrees of Bachelor of Science and Doctor of Medicine from the University of Michigan. From 1894–98, he was in charge of a general hospital in Kolgan, China. From 1905–10, he conducted a private hospital in Cody, Wyo. He was later on the staff of the Clifton Springs Sanatorium, of Clifton Springs, N. Y., and Phelps Sanatorium, Battle Creek, Mich. He later joined the staff of the Southern Pacific Hospital at Houston, Texas, and was internist to the Southern Pacific Lines.

Dr. Waples was a member of the Harris County Society, Texas State Medical Association, American Medical Association, and had been a Fellow of the American College of Physicians since 1920.

DR. AUGUSTUS WARREN CRANE

Dr. Augustus Warren Crane (Fellow), Kalamazoo, Michigan, died February 20, 1937, of coronary thrombosis. Dr. Crane was born in Adrian, Mich., in 1868. He received his medical training at the University of Michigan Medical School, graduating in 1894. He was a member and past-president of the American Roentgen-Ray Society, a member of the Radiological Society of North America, a member of the American College of Radiology, an honorary member of the London Roentgen-Ray Society, a member and past-president of the Kalamazoo Academy of Medicine and Michigan Association of Radiologists. In 1921 he was awarded the gold medal by the Radiological Society of North America. He was a former acting editor and later a member of the editorial board of the *American Journal of Roentgenology*. Kalamazoo College and the University of Michigan both honored him by conferring honorary degrees upon him. He was chairman of the Kalamazoo County Section of the Michigan State Committee of Medical Preparedness, and was a member of Michigan Medical Advisory Board during the World War.

DR. JAMIE W. DICKIE

Dr. Jamie W. Dickie of Southern Pines, N. C., was born near Henderson, N. C., October 25, 1893, the son of George T. and Manolia Coppedge Dickie. He graduated from Wake Forest College in 1914, receiving his

doctor's degree from Jefferson Medical College in 1917, and immediately joined the U. S. Navy Medical Corps, and was stationed at Fort Lyons, Colorado. He received his discharge in 1919, and for two years became associated with the late Dr. W. L. Dunn of Asheville, specializing in pulmonary diseases.

He then went to Southern Pines, N. C., where he established Pine Crest Manor Sanatorium, which has been in successful, continuous operation since. This institution is devoted to the study and treatment of pulmonary diseases.

Dr. Dickie did postgraduate work on many occasions, having spent the entire past winter at the University of Pennsylvania and at Peter Bent Brigham Hospital in Boston. He had only returned to his work a few days when he was taken with pneumonia from which he died July 6, 1937.

His publications were not numerous, and were on subjects related to the chest. As an avocation, however, he wrote short stories and poems, and was widely interested in literature, particularly biography.

He was a member of his County and State Medical Societies, a Fellow of the American Medical Association, and became a Fellow of the American College of Physicians in 1936. He was a director of the North Carolina Tuberculosis Association and a member of the National Tuberculosis Association.

He was a member of the Episcopal Church. He leaves in addition to his wife, who was Miss Inez Benthall, a son, David Henry, and one daughter, Jane.

Dr. Dickie was a man of great personal charm, of good judgment and wide knowledge in his chosen sphere of medical activities, and his sudden passing at an all too early age will leave a gap in the medical profession of this section that will be hard to fill.

C. H. Cocke, M.D., F.A.C.P.,
Governor for N. Carolina